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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1957

ORIGINAL ARTICLES

CLINICAL STUDIES ON A VASOPRESSOR AGENT: METARAMINOL (ARAMINE)*

III. OBSERVATIONS ON ITS ORAL USE IN THE TREATMENT OF HYPOTENSION

By Max H. Weil, M.D.†
RESEARCH FELLOW IN MEDICINE

(From the Department of Medicine, University of Minnesota Medical School and the Medical Service, University Hospitals, Minneapolis, Minnesota)

In studies already reported[8,9], the usefulness of metaraminol in the treatment of patients with shock and hypotensive states was investigated. On the basis of the favorable results noted, this agent became the pressor amine of choice at the University of Minnesota Hospitals, where it has been used in the treatment of more than 500 patients. This extensive experience with the parenteral use of metaraminol clearly has established its potent and sustained action, the practicality of prolonged use and its reassuring freedom from toxic side effects. These findings were corroborated by clinical studies recently reported from two other medical centers (Moyer and Beazley[4] and Stechel *et al.*[7]).

Metaraminol, unlike epinephrine and norepinephrine (levophed), is effective by the oral as well as by the parenteral route. In this respect, it resembles ephedrine and r-amphetamine (benzedrine). However, the pharmacologic activity of metaraminol, like norepinephrine, is primarily vasopressor and does not include the anorexigenic or cardioaccelerator effects or the stimulating effects on the central nervous system produced by ephedrine or r-amphetamine. The structural relationships of these compounds are shown in Fig. 1. It will be noted that effectiveness of these agents when given orally is associated with the presence of a methyl group on the alpha carbon atom and the absence of a hydroxyl group in the para position of the phenyl ring.

The present clinical studies were done to evaluate the vasopressor activity of metaraminol when it is given orally to humans. Previous studies on dogs showed that metaraminol is absorbed rapidly from the gastrointestinal

*Metaraminol was generously supplied as aramine bitartrate by the Merck, Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., West Point, Pa.

†Present address: Mayo Foundation, Rochester, Minnesota.

tract and that a dependable and prolonged increase of systemic blood pressure results when the drug is administered orally (Siegmund, Nash and Granger[5]). Because of the difficulty of studying the effect of these agents on patients with a constantly changing picture of hypotension, observations were made initially on normotensive volunteers. Its clinical effectiveness in various hypotensive states was explored subsequently.

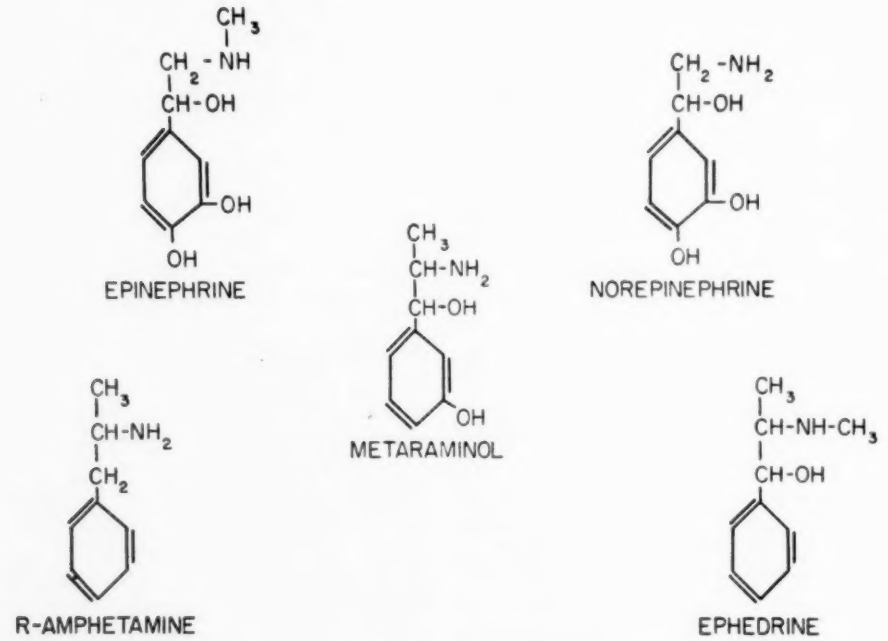

Fig. 1.—Structural relationships among commonly used sympathomimetic drugs.

Observations on Normotensive Persons. METHOD OF STUDY. Single doses of metaraminol were administered orally to 16 normotensive fasting volunteers. These persons were instructed and encouraged to report all subjective effects that followed. Blood pressure was measured by means of a standard mercurial sphygmomanometer with the persons in the sitting position. The pulse was counted by cardiac auscultation. Blood pressure and pulse were measured at intervals of 5 to 15 minutes. An increase in pressure of at least 20 mm. of mercury systolic or 10 mm. diastolic above the baseline value arbitrarily was regarded as evidence of a pressor response.

RESULTS. Pressor Response. A pressor effect was not obtained with oral doses of less than 30 mg. However, a prolonged pressor effect proportional to the dose was observed in 8 of 10 volunteers when 30 to 45 mg. was administered. The onset of the pressor response occurred at approximately 45 minutes and a maximal pressor effect rapidly was established at approximately 1 hour. Pressor activity persisted for 2 to 3 hours after administration and the duration was prolonged when the dose was increased. These results are summarized in Table 1 and Fig. 2.

CARDIAC RATE AND RHYTHM. Sinus bradycardia with a decrease of the pulse rate of as much as 30 beats per

minute occurred in 9 persons. Variable degrees of sinus arrhythmia also were noted in most volunteers. These reflex vagotonic effects were related closely to the pressor effect. Electrocardiographic evaluation of this manifestation has been reported previously in connection with studies on the parenteral administration of metaraminol[9].

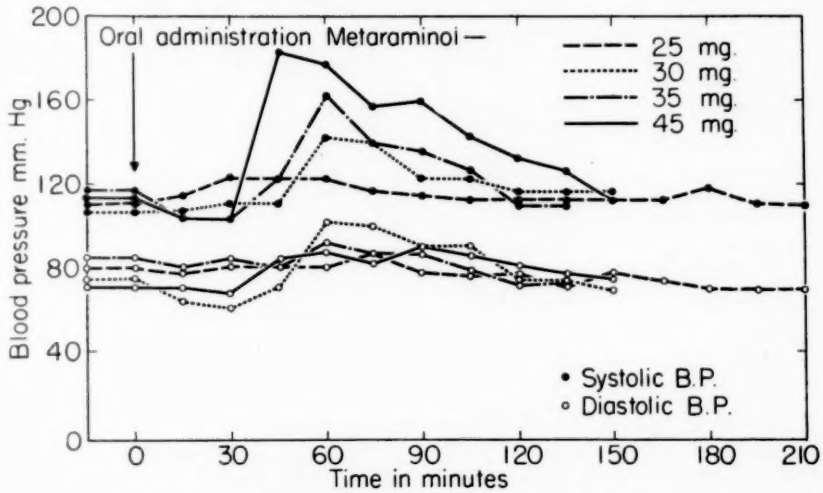

Fig. 2.—Response of blood pressure in normotensive volunteers after oral administration of various doses of metaraminol.

TABLE 1.—AVERAGE DURATION AND INTENSITY OF PRESSOR EFFECT OF METARAMINOL GIVEN ORALLY IN NORMOTENSIVE VOLUNTEERS

No. Persons	*Oral Dose, mg.*	*Onset of Pressor Effect**	*Time of Maximal Response**	*Duration of Response**	*Maximal Increase in Blood Pressure, mm.Hg*		*No Pressor Response*
					Systolic	*Diastolic*	
2	15	0	0	0	0	0	2
2	20	0	0	0	0	0	2
2	25	0	0	0	0	0	2
3	30	45	60	83	33	30	1
5	35	52	71	120	42	10	1
2	45	45	65	195	85	40	0

* Minutes after oral administration.

SIDE EFFECTS. Except for severe headache, nausea and vomiting in one person, who had an excessive increase of blood pressure after a dose of 45 mg., significant toxic side effects were not observed. Subjective effects such as "tingling throughout" or a dizzy and "high" feeling occasionally were noted, as they were in studies with injected metaraminol[9].

Observations on Patients With Symptomatic Hypotension. SELECTION OF PATIENTS. Metaraminol, administered orally, was used in the treatment of 26 men and 9 women who had symptomatic hypotension. Studies were limited to patients who were able to co-operate sufficiently so that acceptance of medication presented no difficulty. The princi-

pal symptoms displayed by these patients were weakness, lightheadedness, disorientation, intermittent confusion, fainting and convulsive episodes. Medical services contributed 24 of these 35 patients, whereas 11 were from surgical services. The patients' ages ranged from 40 to 84 years, the median being 64.

METHOD OF ADMINISTRATION. In preliminary studies, it was found that the amount of metaraminol given by the oral route necessary to produce an equivalent pressor effect was approximately six times that given intramuscularly or subcutaneously. When the oral route was decided on for a patient with prolonged hypotension who had been receiving medication parenterally, five times the amount given parenterally was employed. Administration was repeated at intervals of 1 to 3 hours depending on the character of the response; the dose was altered by 5 to 10 mg. when necessary in order to achieve the desired clinical response and changes in blood pressure.

When oral vasopressor therapy was begun in patients who had not received parenteral therapy previously, an initial dose of 15 mg. of metaraminol was selected and the amount was increased by increments of 5 to 10 mg. until the desired effect was produced. When the pattern of response for a given patient had been well established, only occasional determinations of blood pressure were necessary. Administration at intervals of 1½ hours proved satisfactory for a majority of the patients. During recovery, a gradual reduction in the size of doses preceded discontinuance of therapy.

In patients with chronic postural hypotension, which in every case was associated with a neurologic disorder, doses of 10 mg. were used initially and this amount was increased by 5-mg. increments. Particular care was necessary with respect to dosage because unusual vasopressor sensitivity was common in this group of patients. The first dose of the day was given 1 hour before the patient arose and medication was discontinued 1 to 3 hours before retiring. Because of the dangers of hypertension on recumbency, rest in bed during the day was discouraged.

For patients who were fed by gastric tube, tablets of metaraminol were dissolved in 15 to 30 ml. of water and administered through the tube.

RESULTS. The results for the entire group of patients are summarized in Table 2. An "excellent response" indicated prompt establishment and maintenance of essentially normal systemic arterial pressure with control of symptoms. A "satisfactory response" indicated establishment of a systolic blood pressure of more than 100 mm. of mercury, with satisfactory maintenance and symptomatic improvement. A "poor response" indicated that the pressor effect was inadequate or erratic and therapy produced no symptomatic improvement.

Of the 35 patients treated, 25 had been maintained on parenteral therapy with metaraminol before oral therapy was substituted, and thus the pretreatment blood pressures did not reflect the full severity of their hypotensive state. Several urologic patients had essential hypertension before the onset of hypotension and, therefore, relatively higher blood pressures were necessary to produce satisfactory therapeutic results.

An excellent or satisfactory response was obtained in 32 patients (91%). The average oral dose was 25 mg., indicating that these patients were responsive to a much smaller oral dose of metaraminol than were the aforementioned volunteers. The largest total daily dose given to a patient who recovered was 1,120 mg. Except for one patient, who received this agent continuously for 10 months, the average duration of treatment was 8.5 days. After the appropriate dosage in individual cases had been established by trial, satisfactory constancy of effect usually was maintained, with only minor fluctuations in blood pressure.

Nine of the 35 patients ultimately died, and necropsy was done in 7 instances. In each case, hypotension was merely a manifestation of a serious underlying condition that progressed to fatal termination.

The 8 patients who had chronic postural hypotension deserve particular mention. Rehabilitation resulting in

control of symptoms without medication was achieved in only 3 of these 8 patients. Two patients died while under treatment. Long-term treatment of 2 patients was discontinued because of gastrointestinal side effects. As already indicated, one patient with strikingly severe postural hypotension has received the drug for more than 10 months, with eminently satisfactory results.

TABLE 2.—RESULTS OF ORAL USE OF METARAMINOL IN HYPOTENSION: 35 CASES

Cause of Hypotension	*Cases*	*Average Blood Pressure, mm. Hg*		*Response*			
		Before Therapy	*After Therapy*	*Excellent*	*Satisfactory*	*Poor*	*Survivors*
Infection	10	87/52	123/67	2	7	1	7
Bacteremia	6						
Systemic infection	2						
Malaria (therapeutic)	2						
Urologic procedures	8	96/53	139/70	2	5	1	7
Postural (orthostatic) hypotension associated with neurologic disorders	8	84/28	123/74	3	5	0	6
Diabetes mellitus	2						
Neurovascular syphilis	2						
Spinal-cord transection (traumatic)	1						
Vertebral-artery thrombosis	1						
Idiopathic orthostatic hypotension	2						
Myocardial infarction	3	85/47	120/60	1	2	0	2
Miscellaneous	6	85/53	118/67	2	3	1	4
Postoperative hypotension	2						
Pulmonary embolism	1						
Transfusion reaction	1						
Constrictive pericarditis	1						
Pulmonary emphysema, cardiac failure	1						
Totals	35	88/41 (average)	124/69 (average)	10	22	3	26

SIDE EFFECTS AND TOXICITY. No serious toxic side effects were noted. Loose stools occurred in 4 patients and epigastric distress in three. These gastrointestinal symptoms occurred with much greater frequency in patients who had chronic rather than transient hypotension. As already stated, discontinuance of treatment was necessary in 2 patients who had chronic disability. Administration of metaraminol immediately before or less than 1 hour after meals resulted in delayed pressor response in only two instances. A cumulative effect leading to an exaggerated increase in blood pressure followed. However, this was obviated by scheduling medication at least one-half hour before or 1 hour after meals. In contrast to the effect observed in volunteers, reflex vagal slowing of the heart was not observed ordinarily in these patients.

Case Reports. CASE 1. A 52-year-old man had had severe idiopathic orthostatic hypotension for more than 4 years, with defective sweating below the nipple line and orthostatic bradycardia. The systolic blood pressure in the supine position was approximately 80 mm. of mercury and rapidly decreased to lower values when the patient sat up. Hemi-

plegia had resulted from a cerebrovascular accident 1 year earlier and an ill-defined neurologic disability resembling paralysis agitans had become apparent.

The patient has received 10 to 20 mg. of metaraminol by mouth at approximately 2-hour intervals for 10 months. Without medication, he was lethargic and confused, and was unable to maintain a sitting position without fainting. He is still unable to walk because of his neurologic disabilities but he remains alert and tolerates the sitting position without fainting. The pressor effect obtained in this patient is illustrated by a representative segment of his blood-pressure record (Fig. 3).

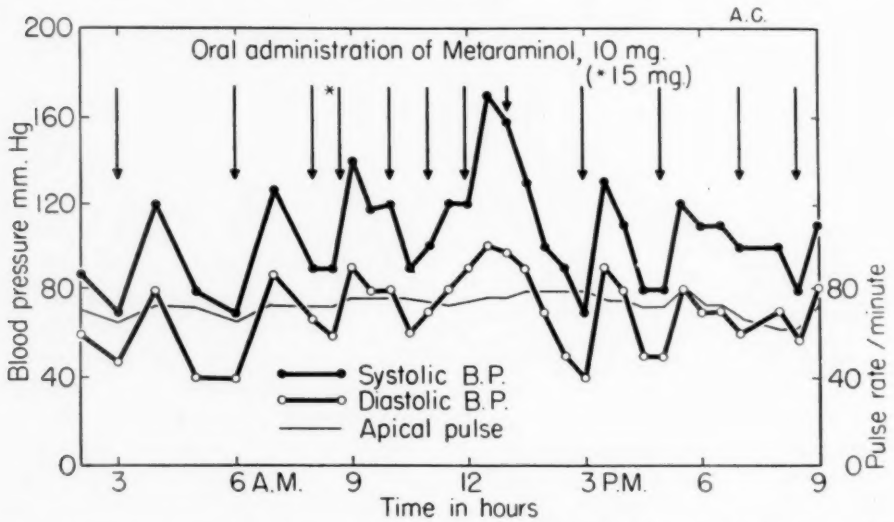

Fig. 3.—(Case 1). Segment of record of blood pressure and pulse taken in the sitting position during treatment of a patient with severe postural hypotension associated with neurologic disease.

CASE 2. A 64-year-old man sustained an intertrochanteric fracture of the femur after a fall. Internal fixation was performed with the patient under spinal anesthesia. Severe postural hypotension was noted early in the postoperative period, and fainting occurred whenever the head of the bed was elevated more than 45 degrees.

The blood pressure was supported with metaraminol in doses of 40 mg. each hour, by mouth, allowing him to tolerate the sitting position without difficulty. Increase in dose to 75 mg. given one-half hour before arising allowed ambulation and graded exercises for muscular rehabilitation without acute hypotension and loss of consciousness. Gradual improvement took place; after 50 days of intensive rehabilitative efforts, the response of the blood pressure to changes in posture was adequate without vasopressor support.

CASE 3. A 58-year-old man manifested hypotension 6 hours after the clinical onset of acute posterior myocardial infarction. Metaraminol was administered by mouth in an effort to maintain the systolic blood pressure above 90 mm.' (Fig. 4). The patient received continuous oral therapy with metaraminol in doses of 15 to 25 mg. every 1 to 3 hours for the first 3 days, and occasional small doses were given subcutaneously for an additional 3 days. The preinfarction blood pressure of 120/80 gradually was re-established and remained stable during the remainder of an uneventful period of recovery.

Comment. When the period of recovery from neuromuscular disease, prolonged rest in bed, operation or severe infection is complicated by symptomatic hypotension, the oral use of metaraminol would appear to be useful. The blood pressure is effectively supported with doses of 10 to 75 mg. repeated at intervals of 1 to 3 hours while ambulation, passive and active

exercises and other techniques of muscular rehabilitation are used to hasten return of normal blood-pressure responses (Judson[1]). The head of the bed may be elevated in severely disabled patients without the production of fainting. The "head up" position described by MacLean and Allen[3] has been a particularly valuable method of treatment in such patients.

In myocardial infarction, when hypotension is protracted and not complicated by gastrointestinal disturbances, the oral use of metaraminol appears to offer practical advantages in therapy. It is atraumatic and convenient. Its prolonged action reduces the frequency with which these critically ill patients need to be aroused.

The results of treatment in patients who have chronic postural hypotension associated with neurologic disorders have not been uniformly good, although striking benefit after prolonged oral therapy with metaraminol was noted in one instance (Case 1). In each patient, excellent control of blood pressure was achieved and orthostatic fainting was controlled. However, gastrointestinal side effects occurred in almost half the patients in this group. Two of the patients died not long after satisfactory control of severe chronic postural hypotension had been achieved. In both instances, the patients had diabetes mellitus of long standing with severe vascular and neurologic complications. Death probably resulted from myocardial infarction, although necropsy was not performed in either of these cases. Sieker and associates[6] recently noted 2 deaths in 10 patients with chronic postural hypotension shortly after improvement in symptoms was achieved with a counter-pressure garment. It appears likely that successful treatment permits a considerable increase in physical activity, which may be tolerated poorly. This would be particularly pertinent in patients with diabetes mellitus in whom the incidence of coronary atherosclerosis is inordinately high

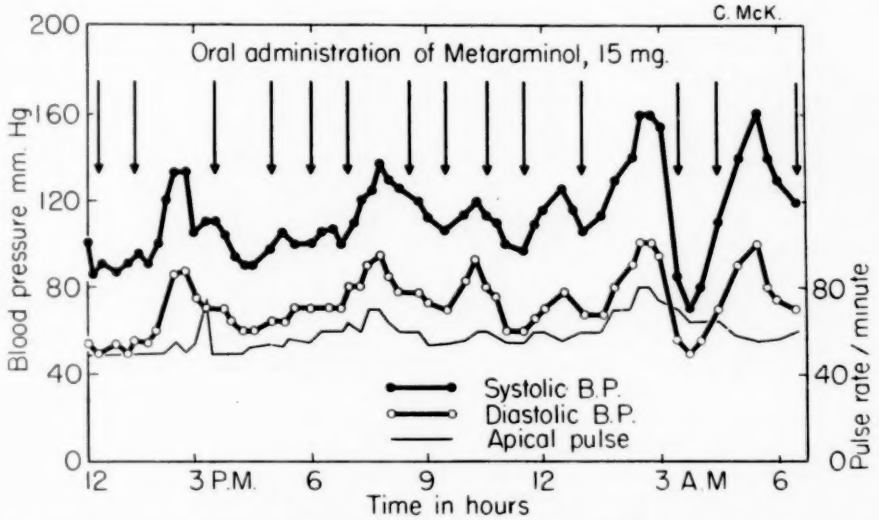

Fig. 4.—(Case 3). Segment of record of blood pressure and pulse in a patient who had myocardial infarction treated with orally administered metaraminol.

(Liebow, Hellerstein and Miller[2]). The invalidism that follows the development of a severe degree of postural hypotension may well protect them against the early development of myocardial infarction. While the use of effective agents like metaraminol in patients with disabling chronic postural hypotension often deserves trial, both the long-term benefits and the dangers involved in such therapy require further investigation.

Summary and Conclusions. Single doses of metaraminol (aramine) were given to 16 normotensive volunteers in a preliminary study of the action of this vasopressor agent when administered by the oral route. The vasopressor effect that followed an adequate dose was potent and prolonged and side effects were negligible. The effective oral dose was five to six times the amount necessary with subcutaneous and intramuscular injection.

Metaraminol subsequently was given orally in the treatment of 35 patients who had symptomatic hypotension from various causes. The response to therapy indicated that this method of administration is practical, effective and safe in most instances. Its value was particularly apparent in patients who had delayed recovery from hypotension associated with systemic infections, myocardial infarction, prolonged rest in bed or after surgical procedures. Treatment of patients who had chronic orthostatic hypotension of the idiopathic type and postural hypotension related to neurologic disturbances was less successful, and the findings indicate that treatment in such patients, although sometimes strikingly rewarding, is more difficult and not without risk.

ACKNOWLEDGMENTS: For constant guidance, the author again is greatly indebted to Dr. Wesley W. Spink. The kind co-operation of colleagues in the Medical Services of Minneapolis General Hospital and Veterans Hospital in Minneapolis and Ancker Hospital in St. Paul, and the assistance of Miss Joan Meyer, R.N., are gratefully acknowledged.

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(Interlingua on page 475)

QUANTITATION OF THE ACTIVITY OF RHEUMATOID ARTHRITIS
6. CORRELATION OF SYSTEMIC AND JOINT FINDINGS

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We have previously described two new methods for quantitating and summing up the manifestations of rheumatoid arthritis, which will now be referred to respectively as the "Articular Index"[3] and the "Systemic Index"[2]. In this paper we record a correlation between the two which strongly supports our previous claim that the Systemic Index measures the activity of the disease with acceptable accuracy.

The Articular Index, based on the area of the articulating surfaces, permits an accurate summation of all measurable joint findings. Thus, it can give the per cent of total possible joint involvement, or a summation of the constituent items, such as: total amount of restricted motion, total amount of structural changes as determined by clinical or roentgenographic techniques, or total amount of joint inflammation. Unfortunately there is as yet no generally accepted, objective method for measuring *degrees* of inflammation which is applicable to *all* joints. This makes it difficult to assess the general inflammatory activity of the disease from a summation of joint inflammation alone. For this reason we have relied on the Systemic Index as a measure of the severity of the disease.

The Systemic Index sums up those general manifestations which can be objectively measured (stiffness, fatigue, aspirin need, grip strength, and sedimentation rate). In support of its validity, we cite the proved observability of its component items[2], and the regular trends of graphed data on cases proceeding to a remission compared with those pursuing a steady course[2]. Further confidence in the accuracy of the Index has been provided by subsequent unpublished observations on the course of numerous cases over a period of 1 to 2 years which appear faithfully to reflect clinical fluctuations in the intensity of the rheumatoid process. In fact, the senior author remembers no clear-cut instance in which a significant change in the index did not confirm his own, or the patient's impression of a change for better or worse.

Nevertheless, the accuracy of the Index of Systemic Activity has so far been tested only by indirect methods or against clinical impressions. For a more conclusive test we needed an independent index which was related to the disease and yet did not specifically include any of the elements of the Systemic Index. Observations on both indexes would then be recorded as pairs, both values being reported for the same patient-interview. Many such pairs were required.

A search of the senior author's

records revealed data on 80 patient-interviews which were converted to index scores for both the Systemic Index and the Articular Index. These pairs are plotted in Fig. 1.

Because of the great individual variation between the severity of the disease and the extent of articular involvement, it had been assumed that the relationship between the indexes might not be well defined. However, the graphed data presented in Figs. 1 and 2, while confirming the considerable variation in individual cases, nevertheless reveal a high degree of correlation between the "activity" and the "spread" of the disease.

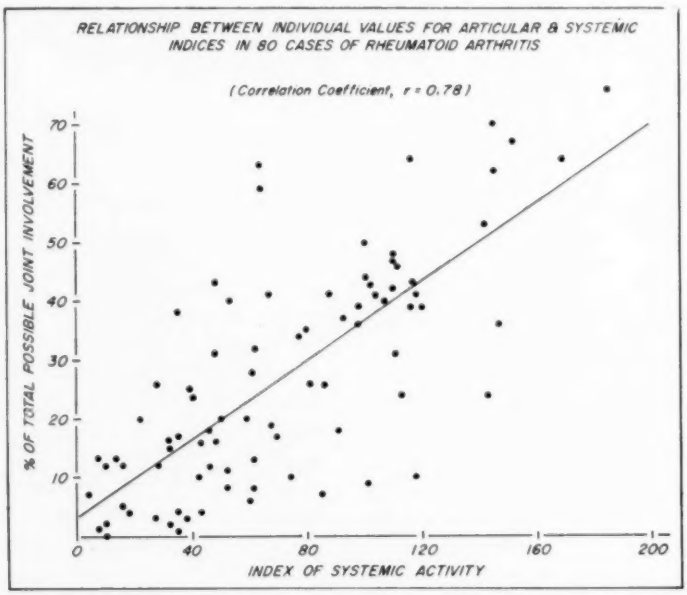

Fig. 1.—Data from 80 unselected cases of rheumatoid arthritis. All observations of the Systemic Index and the Articular Index were made simultaneously on each patient. (In this study the Articular Index takes into account only the presence or absence of arthritis in each joint, no attempt being made to grade the severity of the process.) The scattergram shows a strong clinical relationship between the Systemic Index and the Articular Index. From a statistical viewpoint, the correlation coefficient was $r = 0.78$, which is highly significant (greater than $P = .01$). The line drawn through the data was fitted by the method of Bartlett[1] which takes into account the inherent biological variation in both indexes. The formula for this line is: Articular Index $= 3.64 + 0.33 \times$ (Systemic Index).

In attempting to draw conclusions from this correlation, it should be emphasized that the Systemic and Articular Indexes respectively measure two quite different things. The Systemic Index, and its component items, all measure *gradations of intensity* of the rheumatoid process, whereas, the Articular Index was here used to sum up the total "amount" of joint involvement and took into account only the presence or absence of such involvement *without any reference to gradations in intensity of articular inflammation.* This type of joint evaluation seems to be as simple and objective as is possible and so provides a really

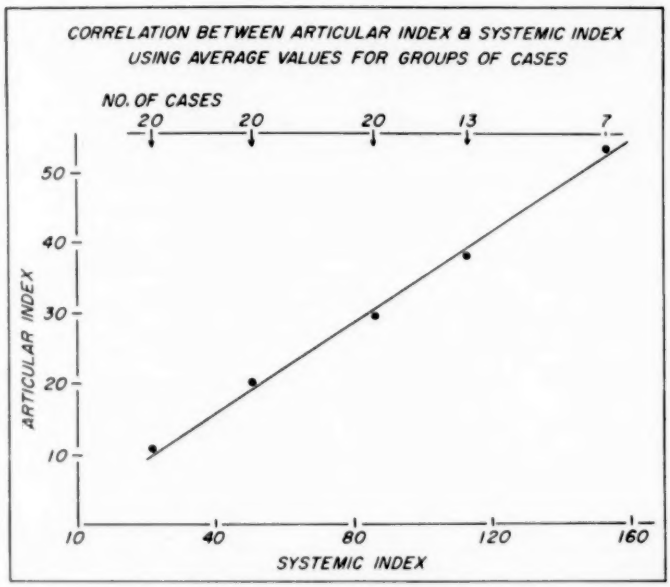

Fig. 2.—Using the same individual observations as were used in Fig. 1, the average values for groups of cases (as noted) were determined. These averages are based on the Systemic Index and the corresponding values for the Articular Index are plotted against them. Since the Articular Index is probably the simplest and most objective clinical observation that can be made on a rheumatoid patient, the plotted averages indicate a high degree of reliability for the Systemic Index for the full scale of values recorded here.

CASE OF MRS. E.A.K. OBSERVED OVER 17 MONTHS
MONTHS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
SEVERE MENORRHAGIA
120
100
80
60
40
20
--- ARTICULAR INDEX X3.15 Without reference to grading of severity of joint inflammation. All observations made simultaneously.
— SYSTEMIC INDEX

Fig. 3.—Shows parallelism between the Systemic and Articular Indexes in a single case going into remission. (This does not imply that an equal parallelism would be found in other cases.)

sound basis for comparing the accuracy of the Systemic Index.

Our main conclusion is that a high degree of correlation exists between the amount of joint involvement and the intensity of the general or systemic manifestations of the disease. Thus, the clinical reliability of the Systemic Index parallels the reliability of the joint findings.

From the point of view of clinical use, the two Indexes should be kept separate, since they furnish independent pieces of useful information on each individual case. In Fig. 3 we present data on both Indexes in a case going into remission over a period of 17 months. A good degree of parallelism between the two is obvious. However, this is the only case in which we have made such extended observations, and we are particularly anxious not to claim that a similar parallelism will be found in other cases. The graph simply shows that such a correlation *can* exist.

Summary and Conclusions. 1) The accuracy of the previously described Index of Systemic Activity of Rheumatoid Arthritis has hitherto been judged only by indirect methods and by clinical impressions.

2) Simultaneous, paired observations of the Systemic Index and the Articular Index on 80 unselected cases of active rheumatoid arthritis show a striking correlation (Coefficient = r = 0.78).

3) The Articular Index is based on the simplest, most reliable type of clinical observation. Its high correlation with the Systemic Index therefore indicates an equally high degree of reliability for the latter.

4) The Systemic and Articular Indexes can now, therefore, be recommended as rapid and acceptably accurate methods for recording the activity, and summing up the joint findings, of rheumatoid arthritis.

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SUMMARIO IN INTERLINGUA

Quantitation del Activitate de Arthritis Rheumatoide 6. Correlation de Constatationes Systemic e Articular

1. Le accuratia del previemente describite Indice de Activitate Systemic de Arthritis Rheumatoide ha usque nunc essite judicate solmente per methodos indirecte e super le base de impressiones clinic.

2. Simultanee observationes parallel del Indice Systemic e del Indice Articular in 80 nonseligite casos de active arthritis rheumatoide monstra un correlation frappante. (Coefficiente = r = 0,78.)

3. Le Indice Articular es basate super le typo le plus simple e le plus digne de confidentia de observationes clinic. Su alte correlation con le Indice Systemic indica per consequente un alte grado de fidelitate in iste ultime.

4. Assi le Indices Systemic e Articular pote nunc esser recommendate como rapide e adequatemente exacte methodos pro le registration del activitate de arthritis rheumatoide e pro le summarisation del constatationes articular in iste condition.

RESPIRATORY AND CARDIAC DEATHS IN LOS ANGELES SMOGS

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There is developing today a new type of community health hazard associated directly with the irritating ozone (or oxidant) smogs shown by Haagen-Smit[4] to arise largely from the action of sunlight upon atmospheric mixtures of the unburned hydrocarbons and nitrogen oxides derived from liquid-fuel motor exhausts. This ozone-type smog appeared first in Los Angeles over a decade ago, but it is now beginning to afflict other American urban communities also. It, therefore, becomes important that the community health hazards associated with it be evaluated as closely as possible and that necessary remedial steps be taken. It is closely associated with windless periods of temperature inversion when polluting materials are held trapped in the ground layers of a cloudless atmosphere and subjected to direct sunlight.

It is obvious that maximal allowable pollution of community atmospheres should be kept below the exposed population's sickness and death threshold. Such threshold limits for many pollutants have been carefully worked out for industrial in-plant workers; workmen's compensation laws have made this almost mandatory by holding management liable for any such worker health damage. Such limits have never been determined for outside community populations, however, nor can the limits established for 8-hour daily in-plant exposure of healthy workers be transposed safely to the 24-hour day-after-day exposure of community residents. Discussion of this point at one symposium[9] brought out hints that the in-plant limits are probably 4 to 20 times higher than those to be considered safe for continuous community exposure. This is especially true where the polluting materials possess irritating effects upon the air passages which lead to progressive and accumulative damage.

In order to be doubly certain that Los Angeles-type smogs carry a significant hazard to community life, we have given careful reappraisal to the 1947–1949 Los Angeles data discussed briefly in a former publication[5]. Also these older findings have been strongly reinforced and broadened by the addition of data from more recent years (1953–1955). It now seems clear that residents of the Los Angeles area are facing very considerable and serious respiratory hazards in breathing their smoggy air at its present levels of pollution. These hazards seem to arise mainly from the presence within their atmospheric "mixing bowl" of ozone or total oxidant concentrations now recognized as dangerously irritative to plants and to the human air passages.

Table 1 presents a general month-by-month summary of the 1947–1949 data on day-by-day respiratory and cardiac deaths in Los Angeles as related to the Stanford Research Institute's smog index[7]. The data on deaths were supplied by the California State Department of Health and the smog index information was supplied by the Stanford Research Institute in the form of a continuous graph.

In order that the 1947–1949 death

data of Table 1 might be subjected to unified correlation with the smog index, such correction was applied to all daily death numbers in each month as would bring that month's average for its nonsmoggy days to 42. Such correction to uniform base for the whole 3-year period erases seasonal and temporal changes unrelated to smog episodes while leaving undisturbed all incidental day-to-day variations and those associated with smoggy periods.

Preliminary examination of the corrected death data indicated insignificant changes in daily numbers of deaths so long as the smog index did not rise above 5, hence we classified as nonsmoggy all days with an index of 5

TABLE 1.—RESPIRATORY AND CARDIAC DEATHS IN LOS ANGELES SMOGS.

Year and Month	*Nonsmoggy (SRI Index, 0–5)*		*Moderately Smoggy (SRI Index, 6–9)*			*Severely Smoggy (SRI Index, 10 or Over)*		
1947	*No. of Days*	*Daily Deaths*	*No. of Days*	*Daily Deaths*	*Total Excess*	*No. of Days*	*Daily Deaths*	*Total Excess*
Jan.	29	52.5	0	0	0	2	50.5	— 4.0
Feb.	26	49.5	1	58.0	+ 8.5	1	44.0	— 5.5
Mar.	31	43.7	0	0	0	0	0	0
Apr.	29	41.6	0	0	0	1	63.0	+21.4
May	29	40.0	0	0	0	2	47.0	+14.0
June	30	36.8	0	0	0	0	0	0
July	26	38.3	1	34.0	— 4.3	4	42.8	+18.0
Aug.	31	38.6	0	0	0	0	0	—0
Sept.	22	38.6	5	35.4	—16.0	3	40.7	+ 6.3
Oct.	29	38.6	0	0	0	2	35.0	— 7.2
Nov.	28	44.2	1	58.0	+13.8	1	58.0	+13.8
Dec.	31	52.7	0	0	0	0	0	0
Year	341		8		+ 2.0	16		+73.5
1948								
Jan.	29	61.5	1	82.0	+20.5	1	80.0	+18.5
Feb.	29	50.5	0	0	0	0	0	0
Mar.	31	47.5	0	0	0	0	0	0
Apr.	30	44.0	0	0	0	0	0	0
May	30	40.0	1	48.1	+ 8.0	0	0	0
June	30	39.2	0	0	0	0	0	0
July	26	37.2	5	34.2	—15.0	0	0	0
Aug.	24	37.1	5	36.0	— 5.5	2	41.0	+ 7.8
Sept.	15	34.3	4	39.0	+18.8	11	39.1	+52.8
Oct.	23	37.8	6	35.2	—15.6	2	43.0	+10.4
Nov.	26	42.0	3	35.7	—18.9	1	42.0	0
Dec.	31	50.4	0	0	0	0	0	0
Year	324		25		+ 2.3	17		+89.5
1949								
Jan.	31	54.7	0	0	0	0	0	0
Feb.	25	54.4	3	57.3	+ 8.7	0	0	0
Mar.	30	51.0	1	68.0	+17.0	0	0	0
Apr.	20	45.6	9	46.9	+11.7	1	53.0	+ 7.4
May	29	43.0	1	52.0	+ 9.0	1	52.0	+ 9.0
June	27	42.7	3	45.7	+ 9.0	0	0	0
July	28	42.1	2	44.5	+ 4.8	1	40.0	— 2.1
Aug.	16	42.7	13	43.8	+14.3	2	39.5	— 6.6
Sept.	14	40.8	7	44.3	+24.5	9	49.0	+73.8
Oct.	22	44.3	5	46.2	+ 9.5	4	53.5	+36.8
Nov.	17	45.7	5	45.8	+ 0.5	8	45.1	— 4.8
Dec.	26	50.4	3	56.3	+17.7	2	50.5	+ 0.2
Year	235		52		+126.7	28		+113.7

(See References 5 and 7 for details)

or less, as moderately smoggy those with an index of 6 to 9, as severely smoggy those with an index of 10 or greater.

In Table 2 it is shown that moderately smoggy days had slightly more respiratory and cardiac deaths than did the nonsmoggy, but this increase in smog deaths reached truly significant proportions when the smog index passed the 10 level.

Table 2 also presents results of a similar correlation for the period from August 17, 1953, to December 31, 1954. In this period the day-by-day data included deaths from influenza, pneumonia, bronchitis, asthma, and cardiac conditions (Code numbers 460–502, 5271, 241, 410–422, 434, 440–7). Correlation here was made with daily maximum values for "total oxidant" as supplied by Professor A. J. Haagen-Smit of California Institute of Technology. Since preliminary examination indicated a rise in daily deaths at "oxidant" values above 0.2 ppm in the Los Angeles atmosphere, correlation of "oxidant" values greater than 0.2 ppm and 0.2 or less was made with day-by-day cardiac and respiratory deaths (handled as described above for the 1947–1949 period). Adjustment was made to a nonsmoggy mean of 50 for the "all ages" correlation, to 12 for the "all ages below 65" and to 36 for the "65 and over."

Difficulty was encountered in supplying such equalizing corrections to the 1953–1955 data, for the general worsening of the smog situation has left several of the worst smog months with few or no smog-free days to serve as nonsmoggy controls. Proper correction for such months was obtained by anchoring them to the nearest month with a stable number of smog-free days. Table 3 indicates the derivation of the proper correction factors for use in such cases, such derivation being based upon 5-year average values (death data available for 1955 covered only ages 65 and over).

It has been suggested that the frequent association of smogs with excessive heat may give an erroneously high smog-death correlation, since the excess deaths may have been brought about by heat. It must be pointed out, therefore, that days with a maximum temperature above 96° F. numbered 0 in 1947, 1 in 1948, 4 in 1949, 4 in 1953, and 0 in 1954. Of the 5 days in 1948–1949, one was nonsmoggy and with 6 excess deaths, while the other 4 had a high average SRI smog index of 18 and an average of 12 excess deaths per day. Of the 4 in 1953, one fell in July and outside our period of correlation, while the other 3 had only borderline smog and an average of only 6 excess deaths per day. It is known that severe heat can kill, but severe heat in association with severe smog is still more deadly. The extreme heat period of September 1–4, 1955, has been omitted entirely from our correlations.

It is evident from examination of Table 2 that respiratory and cardiac deaths in Los Angeles County are positively and significantly associated with prevailing atmospheric smogginess above SRI index values of 5 or "total oxidant" values above 0.2 ppm. It seems obvious, therefore, that these limits should represent the maximal degree of pollution allowable from the community health viewpoint. From Table 2 it is seen that this smog hazard applies just as significantly for people below age 65 as for the more elderly.

It is unfortunate that failure to make proper correction for seasonal trends led the State Department of Public Health to state that in their nursing home deaths ". . . the data do not substantiate any such effect . . ." on this ". . . type of patient that would be adversely and immediately affected by

TABLE 2.—STATISTICAL ANALYSIS OF SMOG-DEATH RELATIONSHIP

Smog Index	*Mean No. Day Deaths*	*S.D. of Mean*	*Days*	*Smog Index*	*Mean No. Day Deaths*	*S.D. of Mean*	*Days*	*Diff. of Means*	*Diff. / S.E. Dif.*	X^2
1947–49, All Ages, SRI Smog Index.										
SRI 0–5	41.89	7.18	950	SRI 6–9	43.39	7.33	83	1.50	1.8	0.4
"	"	"	"	10+	45.89	7.26	63	4.00	4.2	12.6
"	"	"	"	6+	44.47	7.52	146	2.58	3.9	7.4
Aug. 17, 1953 to Dec. 31, 1954, All Ages, "Total Oxidant" Basis.										
0–0.2 ppm Ox.	50.02	9.46	229	0.2 ppm Oxidant	52.29	7.89	273	2.27	2.9	4.8
Same Period, All Ages Below 65 Years.										
0–0.2 ppm Ox.	12.22	4.87	229	0.2 ppm Oxidant	13.43	4.56	273	1.21	2.9	5.5
Same Period, All Ages 65 and Over.										
0–0.2 ppm Ox.	36.21	6.38	229	0.2 ppm Oxidant	37.57	6.57	273	1.35	2.34	6.0
Jan. 1 to Sept. 30th, 1955 (Omitting Sept. 1–4), Age 65 Years and Over.										
0–0.2 ppm Ox.	36.11	6.89	129	0.2 ppm Oxidant	38.21	7.95	140	2.10	2.3	1.6
Aug. 17, 1953 to Sept. 30, 1955 (Omitting Sept. 1–4, 1955), Age 65 Years and Over.										
0–0.2 ppm Ox.	36.15	6.70	358	0.2 ppm Oxidant	37.79	7.07	413	1.64	3.3	7.3

TABLE 3.—CORRECTION FACTORS FOR DAILY DEATHS OF SMOG SEASON

	1947	*1948*	*1949*	*1947–9*	*1953*	*1954*	*5-year*	*Correction*
JUNE								
Clear	36.8(30)	39.2(30)	43.0(27)	39.7		51.9(10)	42.7	−1
Smoggy	——	——	45.7(3)			54.1(20)		
JULY								
Clear	38.3(26)	37.4(26)	42.1(28)	39.3		——	42.3	0
Smoggy	41.0(5)	34.2(5)	43.0(3)			58.8(31)	(estimated)	
AUGUST								
Clear	38.6(31)	37.2(24)	42.7(16)	39.5	45.0(5)	44.3(8)	41.4	+1
Smoggy		37.6(7)	43.2(15)		30.0(12)	48.7(23)		
SEPT.								
Clear	38.6(22)	34.1(15)	40.8(14)	37.8	43.0(1)	36.5(2)	38.5	+3
Smoggy	37.4(8)	39.1(15)	47.0(16)		50.2(29)	51.3(28)		

(Figures in parentheses indicate number of days.)

air pollution"[3]. We have extended our above-described technique for the elimination of normal seasonal trends from the day-by-day nursing home deaths listed in their appendix Table 1, leaving the July death numbers undisturbed, adding 1/42 to those of August, 3/42 to those of September, subtracting 3/42 from those of October and 15/42 from those of November. These corrections are in accordance with our Table 3 extended to include October and November. Correlation of the seasonally corrected nursing home deaths with Haagen-Smit's total oxidant values from July 3 to November 21, 1955 (but omitting the period of excessive heat from August 31 to September 8) gave the following results:

13	days,	oxidant	values	under	.2	ppm,	averaged	4.72	deaths.
23	"	"	"	of	.2	to .39 ppm	"	4.95	"
38	"	"	"	of	.4	to .59 ppm	"	5.22	"
41	"	"	"	of	.6	to .79 ppm	"	5.86	"
17	"	"	"	of	.8	ppm and over	"	6.23	"

Calculation of the correlation coefficient on the seasonally corrected nursing home deaths of the whole 132-day period gave: $r = 0.206$, $p = 0.01$, while similar calculation on the 22 uncorrected days of September (omitting the 8 days of excessive heat) gave: $r = 0.191$, $p = 0.04$. Therefore, it certainly cannot be said that ". . . the data do not substantiate any such effects. . . ." Indeed, the strong trend toward a positive and graded association between nursing home deaths and daily oxidant maxima here demonstrated renders it most probable that further extension of the survey period would provide correlation values well beyond the realm of reasonable chance occurrence.

Since the 1949 association was between deaths and the Stanford Research Institute's smog index, and since the smog index is based upon meteorological factors predisposing to smog formation rather than upon actual air analysis of polluting materials, it seems advisable to relate the SRI index directly with actual air analyses. Fortunately Mr. Bartel of the U.S. Rubber Co., has supplied us with ozone maxima for 148 days of 1949[2]. Table 4 indicates the highly significant relationship existing between these ozone values and the SRI smog index values. Correlation coefficient found for 194 days of matching ozone and SRI smog index values was $r = 0.64$, $p = 0\pm$.

Correlation coefficients calculated for certain parts of the series covered in Table 2 gave:

August 17, 1953—December 31, 1954	(502 days)	$r = 0.08$, $p = 0.03$
September only, 1949	(30 days)	$r = 0.949$, $p = 0+$
" " 1953	(30 days)	$r = 0.837$, $p = 0+$
" " 1954	(30 days)	$r = 0.343$, $p = 0.016$

There no longer exists a reasonable doubt that Los Angeles smogs are indeed related to very considerable increases in respiratory and cardiac deaths. In *no* adequate test period were these deaths *less* frequent on smoggy days than on nonsmoggy days; always the mean numbers of such deaths were found to be greater on the smoggy days of every test period. Nor are such excess deaths limited to elderly

people: younger age groups also share significantly in the smog periods.

In sum total, this Los Angeles hazard is represented by 240 excess respiratory and cardiac deaths in the year 1949, by 281 in the last 137 days of 1953, and by 334 in the year 1954. It should be born clearly in mind that this is merely one measurable index of smog damage, that its total of non-fatal ill-health and chronic damage in the respiratory tract must far outweigh these deaths in community importance.

If we add to these Los Angeles findings the Cincinnati survey results, which clearly relate lung cancer incidence to exposure to urban motor exhaust fumes and general urban air pollution[6], we begin to see the outlines of a community hazard calling for the most effective remedial measures available. The Los Angeles situation is indeed so severe and so fraught with health hazards to the area's residents that any pollution control program should be put on the compulsory health basis that alone can provide it with the necessary over-riding authority.

Recent emphasis (Stokinger[8]) has been given to evidences of ozone toxicity for bacteria, molds, experimental animals and human beings, with the result that maximal allowable concentrations considered safe for industrial in-plant workers were lowered in 1954[1] from the former 1.0 ppm to 0.1 ppm (barely detectable by those with a keen sense of smell). Levels of 0.2 ppm definitely increase guinea pig death rates after 7 to 8 months of exposure, while those animals also seem slightly harmed even by 0.1 ppm concentrations after many months of continuous exposure (Wilska[11]). Bacterial and mold growth is inhibited by 0.2 ppm ozone concentrations. Damage to succulent plants begins at 0.1 ppm ozone or oxidant and is severe at 0.2 ppm (Went[10]).

TABLE 4.—RELATION OF SMOG INDEX[7] TO OZONE CONCENTRATION IN AIR[2]

SRI Smog Index	*No. of Test Days*	*Ozone Parts Per 100 Million of Air*			*Diff. Mean*	
		Aver.	*Mean*	*S.D. of Mean*	*S.E. Diff.*	*X^2 Values*
0	23	9.7	13.00	8.21		
1	21	16.0				
2	25	22.8			5.91	22.5
3	12	22.3				
4	15	23.3		9.64		
5	8	28.2	23.36			
6,7	16	35.5			8.08	19.6
8,9	10	37.1				
10+	18	41.6	39.27	10.08		
All	148					

Ozone toxicity manifests itself in animals and people primarily by irritation and swelling in the cells lining the air passages. Such swelling in the smallest air passages next to the lung's air sacs interferes seriously with their proper ventilation and is the direct cause of death. Other toxic materials such as sulfuric acid mists or the oxides of nitrogen may act similarly in the air passages. Just what connection there might be between such cellular irritation and the generation of lung cancer is not known, but it is significant that such toxicity in most cases means direct interference or blockage of many of the intracellular enzymatic and catalytic systems that form the basis of the vital cellular processes.

The evidences of slow respiratory tract damage in healthy animals continuously exposed for months to ozone concentrations as low as 0.2 ppm (or even 0.1 ppm) makes it imperative that respiratory and cardiac sickness and deaths be still more closely examined for the recent years of steadily worsening smogs in the Los Angeles area. Even without any further evidences than is here presented, there seems ample justification for the imposition of a firm smog-control program aimed at the prevention of atmospheric ozone concentrations above 0.2 ppm (and perhaps even lower) when the area shall have reached complete development.

Los Angeles is not the only urban area now afflicted with damaging ozone (or oxidant) smogs arising largely from the unburned hydrocarbons of liquid-fuel motor exhausts. Cincinnati experienced a number of ozone smogs in the Fall of 1956, the one of October 15 estimated to have been close to the 0.5 ppm ozone level at which Los Angeles calls its First Alert. Here would seem to be an urban community health problem of major proportions.

Summary: Ozone or oxidant-type smogs, now known to be formed by the action of sunlight upon stagnant inversion air masses containing unburned hydrocarbons and nitrogen oxides from liquid-fuel motor exhaust fumes, have been present in Los Angeles for more than a decade and are now appearing with increasing frequency in other American cities as the density of motor transport vehicles increases.

Although ozone was formerly considered a harmless (and perhaps beneficial) atmospheric ingredient, it is now recognized that concentrations of it above 0.2 ppm are potentially harmful to exposed plant and animal life. Its maximal allowable limit for industrial in-plant workers has recently been reduced from 1.0 ppm down to 0.1 ppm (barely detectable by a keen sense of smell).

The present report shows a clearly significant association between Los Angeles smogs and rises in day-by-day respiratory and cardiac deaths in the exposed population. There no longer exists a reasonable doubt that this smog-death relationship is real and of significant proportions. The community health hazard thus generated calls for prompt and energetic measures to lessen pollution of urban atmospheres with liquid-fuel motor exhaust gases, as well as establishing the best possible control over all other known polluting sources.

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SUMMARIO IN INTERLINGUA

Mortes Respiratori e Cardiac in Fumo-Nebula de Los Angeles

Le fumos-nebula ozonic o oxydatori, nunc recognoscite como producto del action de lumine solar super stagnante massas de aere in inversion que contine non-comburite hydrocarburos e oxydos nitrogenic ab fumos de escappamento de motores a combustibile liquide, es trovate a Los Angeles depost plus que un decennio e comencia apparer de plus in plus frequentemente in altere citates statounitese in tanto que le densitate del vehiculos de transporto motorisate continua augmentar se.

Ben que ozono esseva considerate in le passato como un ingrediente atmospheric innocue (e forsan benefic), on nunc sape que concentrationes de ozono de plus que 0,2 parte pro million es potentialmente nocive a exponite organismos vegetal e animal. Recentemente le maximo permissibile pro obreros in fabricas industrial ha essite reducite ab 1,0 a 0,1 parte pro million (lo que es a pena detegibile per un acute senso olfactive).

Le presente reporto revela un clarmente significative association inter le fumos-nebula de Los Angeles e augmentos del diurne mortes respiratori e cardiac in le population exponite. Il non es possibile dubitar ancora que il existe un relation inter fumo-nebula e morte e que iste relation es de character significative. Le assi generate periculo de hygiene public require prompte e energic mesuras pro reducer le pollution de atmospheras urban per fumos de escappamento ab motores a combustibile liquide, a parte le establimento del melior regulation possibile de omne altere cognoscite fontes de pollution.

ENEMA-INDUCED POTASSIUM LOSS IN PATIENTS WITH DISEASES OF THE SPINAL CORD AND CAUDA EQUINA*

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In a recent report from this laboratory[3] detailed findings were presented on a man with motor and sensory paraplegia who insidiously developed severe potassium deficiency as a result of repeated and prolonged enemas. Many patients with diseases of the lower spinal cord or lumbosacral nerve roots have evacuation problems similar to those of the original patient studied and are maintained for long periods of time on laxatives or enemas, or both. The present study is a systematic analysis of postenema potassium losses in such patients to determine the frequency with which significant electrolyte loss occurs.

Material and Methods. Enema returns from 8 controls, 10 patients with paraplegia, 18 patients with poliomyelitis and 2 patients with cauda equina lesions were studied. All subjects were adults. Controls were in the hospital for reasons unrelated to intestinal or neurologic disease. The controls had no history or physical signs of neurologic or bowel dysfunction and received single enemas in preparation for intravenous pyelography. Paraplegic patients had partial or total transverse myelopathies with spastic paraplegia, the level of spinal cord damage varying from C_5 to L_3. Patients with poliomyelitis had paralysis of the lower extremities and usually the abdominal muscles as well. Subjects with cauda equina lesions had complete motor and sensory loss below L_3 and L_4 in addition to scattered paralysis above this level due to poliomyelitis (Plum[7]). One of these latter 2 patients was the subject of the previous case report on excessive potassium loss after enemas. This man was the only patient in the series studied more than 6 months after onset of illness; the data on his studies are re-presented in the present report for completeness.

No patient or control subject received laxatives. Both patients and controls were on a general hospital diet containing approximately 75 mEq. potassium per day. The patients with neurological illness required repeated enemas for satisfactory stool evacuations at the time of study; each averaged three enemas weekly. Stool specimens following enemas were selected randomly for analysis without prior notification of nurses that special studies were in progress. Tap water was used for enemas. The amount of fluid infused and the time required for evacuation was measured. Returns were measured, homogenized and wet-ashed following which an aliquot was analyzed for potassium content with a Baird flame photometer. Total stool potassium was then calculated.

Results. Table 1 lists the ranges of stool potassium content found in each group of patients and controls. Averages for potassium loss, volume of enema fluid required to achieve evacuation, and time required to achieve evacuation are given. Figure 1 diagrams individual stool potassium contents for the total series. On the average, pa-

*This study was aided by an annual grant from The National Foundation for Infantile Paralysis, Inc. to the Northwest Respirator and Rehabilitation Center.

tients with spinal cord or lumbosacral nerve root disease who required repeated enemas lost approximately twice as much potassium into their stools as did normal individuals. Average enema stool potassium was 6.6 mEq. in normals, 13.2 mEq. in paraplegics, 14.8 mEq. in patients with poliomyelitis, 12.4 mEq. in one patient with a cauda equina lesion, and 72.0 mEq. in the other. Individual patients within the several groups with neurologic disease were drained of considerable amounts of electrolyte (Table 2). Three patients with paraplegia, 10 with poliomyelitis, and both those with cauda equina lesions had individual postenema stool specimens that contained 20 mEq. or more of potassium. Five of these patients had at least one specimen containing more than 30 mEq. Analyses in several patients of specimens taken

TABLE 1.—RANGE OF STOOL POTASSIUM AFTER ENEMAS

No. Subjects	*Total No. Specimens Analyzed*	*Average Volume Infused*	*Average Volume Expelled*	*Average Time Required*	*Range K Content in Individual Specimens*		*Av K Loss per Specimen*
					Min.	*Max.*	
Normals							
8	8	1000 ml.	1061 ml.	<30″	1.4	10.3 mEq.	6.6 mEq.
Paraplegia							
10	24	1480	1763	39″	0.7	32.3 mEq.	13.2 mEq.
Poliomyelitis							
18	62	1225	1160	37″	0.5	76 mEq.	14.8 mEq.
Cauda Equina							
1	10	2100	1780	70″	11.1	258.5 mEq.	72 mEq.
1	39	1400	1310	50″	0.4	50.2 mEq.	12.4 mEq.

TABLE 2.—POSTENEMA STOOL POTASSIUM LOSSES OVER 20 mEq.

Subject	*Total No. Specimens Measured*	*No. Specimens Containing >20 mEq. K.*	*Maximal Weekly Stool K. Loss*
Paraplegia			
R. W.	5	1: (20 mEq. K)	*
H. L.	6	1: (25.8 mEq.)	*
R. G.	2	1: (32.5 mEq.)	*
Poliomyelitis			
A. W.	7	2: (20.4; 26.4 mEq.)	32.0 mEq.
L. K.	2	1: (20.3 mEq.)	*
R. H.	7	2: (23.5; 20.0 mEq.)	51.2 mEq.
S. J.	3	1: (33.0 mEq.)	*
S. W.	4	3: (22.8; 28.8; 23.2 mEq.)	74.8 mEq.
R. Ra.	7	3: (75.9; 56.2; 40.1 mEq.)	172.2 mEq.
C. A.	1	1: (23.1 mEq.)	*
M. B.	3	1: (27.6 mEq.)	*
J. F.	3	1: (34.0 mEq.)	*
W. G.	2	1: (22.6 mEq.)	*
Cauda Equina			
H. W.	39	8: (22.8; 24.2; 45.6; 31.7; 28.8; 50.2; 25.8; 20.8 mEq.)	84.4 mEq.
R. Ro.	10	7: (258.5; 95.9; 78.8; 32.7; 68.4; 106.0; 43.4 mEq.)	433.2 mEq.

* Weekly loss not calculated

consecutively over several days showed no tendency to conserve potassium on successive evacuations to compensate for high electrolyte loss after a previous enema. Maximal weekly stool potassium losses were heavy in S. W. (74.8 mEq. K), and R. Ra. (172.2 mEq. K) in the group with poliomyelitis as well as in both H. W. (84.4 mEq. K) and R. Ro. (433.2 mEq. K) with cauda equina lesions.

In order to determine whether postenema stool losses depleted total body potassium, Neal[6] studied in detail R. Ra. convalescing from poliomyelitis. Balance studies for potassium during a 3-week period showed a dietary intake of 1434 mEq. K, a urinary output of 1268 mEq. K, and a postenema stool loss of 191 mEq. K. With an estimated skin loss of 4 mEq. K daily (Blahd and Bassett[1]), the total balance for the period was a negative 110 mEq. K. Urinary potassium output never fell below 41 mEq. per 24 hours. Some of the electrolyte loss may have reflected muscle wasting since the study was started 3 weeks after onset of poliomyelitis. Serum potassium gradually declined from 5.5 mEq. per liter to 4.0 mEq. per liter during the study period, however, and the day-night ratio of urinary potassium loss gradually approached unity. This alteration in diurnal variation was noted by Evans *et al.*[4] to be an early development in experimentally induced potassium depletion.

Volumes of fluid required to achieve satisfactory stool evacuation were often higher in patients with neurologic disease than in normals (Table 1). Greater time also usually was required for evacuation of enemas in the patients with neurologic disease so that the duration of contact between electrolyte-free fluid and bowel wall was prolonged. Stool potassium content exceeding 20 mEq. usually resulted when large volumes of infused fluid were associated with a prolonged emptying time.

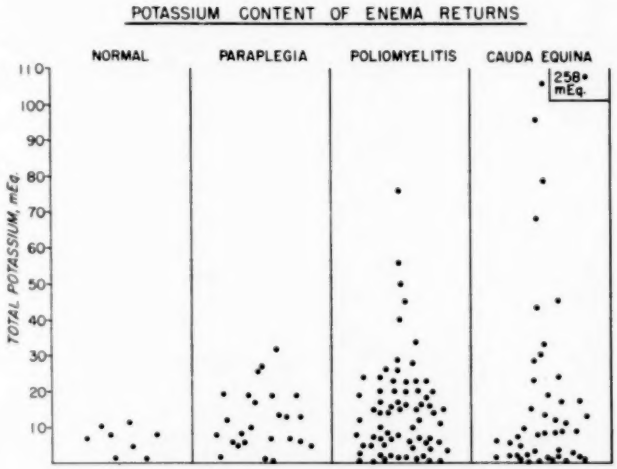

Fig. 1.—Each dot represents the total potassium content of a single postenema stool specimen. All specimens analyzed in each group of patients are included in this graph.

Discussion. Loss of muscle tissue from paralysis results in a marked reduction of total body potassium. Patients with muscle wasting following

"bulbospinal" poliomyelitis studied by the isotope dilution technique have total exchangeable body potassium contents of but 1200 to 1500 mEq. (Blahd *et al.*[2]). Normals, by contrast, have a total of 2900 to 3500 mEq. of exchangeable potassium. A given quantity potassium loss in the paralyzed thus creates a greater percentage loss of total body stores and this may accelerate the rate at which signs of clinical deficiency appear.

General diets usually contain 75 to 100 mEq. K. per day. Anorexia reduces the intake sharply so that no more than 20 to 40 mEq. K may be ingested daily in patients with poor appetites. Urinary potassium excretion varies with dietary intake and, up to a certain point, balances the difference between intake and other sources of loss. Renal excretion of potassium seldom drops below 20 mEq. per day, however, so that efficient conservation is lacking to protect against severe restriction of potassium intake or significant extra-renal potassium losses.

Most patients with lower spinal poliomyelitis, transverse spinal cord lesions or lumbosacral nerve root disease have difficulty in spontaneously emptying their bowels. Laxatives are frequently given, and unless special training in bowel care is undertaken, periodic or recurrent enemas are often necessary. Laxatives increase gastrointestinal potassium wastage, inducing stools with potassium contents as high as 65 mEq. per liter (Schwartz and Relman[8]). Although cathartics were withheld and enemas were limited to a maximum of three per week, 2 subjects with poliomyelitis and both subjects with cauda equina lesions in the present series had weeks when stool potassium losses were 75 mEq. or more. Postenema losses created severe clinical potassium deficiency in R. Ro. and induced a negative potassium balance in R. Ra. In both these latter patients, dietary potassium supplements were required to make up the electrolyte deficit.

Factors contributing to abnormally high stool potassium losses after enemas in neurologic patients appeared to be the large volumes of enema fluid required and the prolonged time taken for evacuation. Abdominal manipulation which sometimes was used to assist fecal expulsion also may have aided electrolyte transfer into bowel contents. Enemas repeated for weeks or months may eventually produce a dilated colon with increased surface area for electrolyte transfer: R. Ro. who had been receiving large volume enemas for over 2 years thus was the patient who suffered the greatest postenema potassium losses. Whether enemas stimulate the bowel wall to secrete fluids high in potassium content could not be determined from the available data.

Bowel training to eliminate enemas in paraplegics previously has been emphasized to reduce needs for nursing care and to increase independence (Munro[5]). The present study demonstrates that an important indication for early bowel training is to minimize stool potassium losses which may become severe if enemas and laxatives are continued indefinitely.

Summary. The potassium content of enema returns was analyzed in 8 normal subjects, 10 patients with paraplegia, 18 patients with poliomyelitis, and 2 patients with cauda equina lesions. The patients required repeated enemas at the time of study but were not receiving laxatives. Average stool potassium was 6.6 mEq. in normals, 13.2 mEq. in paraplegics, 14.8 mEq. in patients with poliomyelitis, and 12.4 mEq. and 72.0 mEq., respectively, in 2 patients with cauda equina lesions. Four

subjects with neurologic disease had weekly stool losses of 75 mEq. K or more. Two patients with high stool potassium losses were in negative potassium balance and one of these developed severe clinical potassium deficiency. Enemas and laxatives, if continued indefinitely, are a potential source of potassium depletion in paraplegic patients.

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SUMMARIO IN INTERLINGUA

Perdita de Kalium, Causate per Clysteres in Patientes con Morbos del Medulla Spinal e del Cauda Equin

Le contento de kalium in le effluvios clysteral esseva analysate in 8 subjectos normal, 10 patientes con paraplegia, 18 patientes con poliomyelitis, e 2 patientes con lesiones de cauda equin. Al tempore del studio le patientes requireva repetite clysteres, sed illes non recipeva laxativos. Le nivellos medie de kalium fecal esseva 6,6 mEq in subjectos normal, 13,2 mEq in paraplegicos, 14,8 mEq in patientes con poliomyelitis, e 12,4 e 72,0 mEq in le duo patientes con lesiones de cauda equin. Quatro subjectos con morbo neurologic habeva perditas septimanal de 75 mEq de kalium o plus. Duo del patientes con alter perditas fecal de kalium se trovava in statos de balancia negative de kalium. Un de illes disveloppava sever grados de carentia clinic de kalium. Clysteres e laxativos, si usate a continuitate indefinite, es un causa potential de depletion de kalium in patientes de paraplegia.

THE RELATIONSHIP OF SERUM SODIUM TO TOTAL SERUM OSMOLARITY: A METHOD OF DISTINGUISHING HYPONATREMIC STATES*

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In human serum the sodium and chloride ions make up the bulk of the total ions present and, as such, are the largest contributing factors to the freezing point depression (Δ^t) of sera of normal persons and of those patients with hyponatremia due to various causes. If the contribution of the serum sodium to the freezing point depression of the sera in pathological conditions is markedly different from normal a laboratory method may be evolved to differentiate types of hyponatremia and suggest proper therapy..

Materials and Methods. Two milliliters of serum was placed in a chemically clean test tube (16 × 120 mm.) and immersed in an ice-water-salt mixture, the temperature of which was between −3° and −4° C. The rim of the tube was attached by a pulley to a Sargent cone drive stirring motor so that the tube was rotated constantly in the bath. A Beckman thermometer† was standardized by determining the freezing point depression of a 0.3 molal glucose solution which was regarded as −0.56° C. The thermometer was placed in the test tube and supported by a ring stand so that it rested approximately 0.5 cm. from the bottom of the tube. While the tube rotated with the cone drive, supercooling was allowed to take place to about 3° below 0° C. At this point the tube was gently elevated and tapped against the bottom of the thermometer which caused crystallization to take place and the maximum rise of the mercurial column after supercooling was read. The average of two determinations was accepted as the freezing point. The whole procedure takes 2 to 3 minutes.

This method does not measure the true freezing point but rather the maximum point of elevation of the temperature after supercooling. It is a highly reproducible method (± 0.01° C.) and approximates the true freezing point when conditions are carefully controlled and all specimens are handled in the same manner. By this method the freezing point of 0.154 molal sodium chloride was found to be −0.53° C. which is in good agreement with the value calculated from data from the International Critical Tables[2].

FREEZING POINT DEPRESSION OF DILUTE SALINE SOLUTIONS. Sodium chloride was made up in various dilutions in distilled water, the freezing point and sodium were determined on each of the dilutions and the results expressed graphically. Presuming equal ionization of sodium and chloride at this concentration the freezing point depression of any particular dilution of the original sodium chloride solution divided by two would equal the freezing point depression caused by the sodium or the chloride ions in that solution. By referring to a graph or a table constructed from the graph (Table 1) it is possible to estimate the contribution of sodium to the freezing point depression for any concentration of sodium between 100 and 170 mEq./L.

*This study was supported in part by a grant from the Wisconsin Heart Association.

†Since these studies were undertaken, the Advanced Instrument Co., Inc., has marketed the Fiske Osmometer which, although calibrated in milliosmols, actually measures freezing point depressions to ± .001° C. However, the Beckman thermometer is simple and satisfactory for measuring freezing point depressions of biological fluids for the calculations in this study.

Ten milliliters of blood was drawn from human subjects in the postabsorptive state. The blood was centrifuged at 10,000 revolutions per minute for a period of 10 minutes. The serum was decanted and was again centrifuged at 10,000 revolutions for 5 minutes. The sodium was determined on each of the sera with a Barclay Flame Photometer using lithium as an internal standard.

Results. FREEZING POINT DEPRESSION OF NORMAL SERA. Freezing point determinations were done on sera of 75 normal people in the postabsorptive state. Their ages ranged from 13 to 93 years of age; 44 were males and 31 females. The mean freezing point depression in this series and by these methods was —0.54° C., with a standard deviation of 0.014. No significant difference was noted between the freezing point of the serum of males as compared with females and also there was no difference in freezing point depression of sera in the various age groups.

CONTRIBUTION OF SERUM SODIUM TO DEPRESSION OF THE FREEZING POINT IN HUMAN SERUM. Twenty-five normal persons were studied to determine the contribution of their sodium to the depression of the freezing point of their sera. Table 2 indicates the sodium concentration in sera of 25 normals in the postabsorptive state. The freezing point depressions of the sera of these patients are noted in column 3. By assuming that the sodium in these normal sera acts in the same manner as the sodium in the saline solution, the depression of the freezing point of these sera due to sodium in each of the 25 normals could be obtained from the table (Table 1) and is listed as such in column 4, Table 2. In these 25 cases the mean contribution of the serum sodium to the total freezing point depression of the serum was 0.44 with a range of 0.42 to 0.46 and a standard deviation of 0.024 (Table 2). Thus, in normal serum the sodium in that serum contributes about 44% of the total freezing point depression or .44 Δ^t serum/Δ^t sodium in serum = 1.00.

DILUTION HYPONATREMIA. Table 3 shows 6 cases of low serum sodium associated with dilution due to intravenous administration of large amounts of electrolyte-free fluids. In these patients the freezing point depression of the serum is in the dilution range (above —0.50° C.) but the sodium in the serum is still contributing its expected 44% to the freezing point de-

TABLE 1.—FREEZING POINT DEPRESSION °C. OF SODIUM IN SOLUTION (NaCl) FOR AMOUNTS RANGING FROM 100 TO 170 mEq./L.

Na	Δt	*Na*	Δt	*Na*	Δt	*Na*	Δt	*Na*	Δt
100	0.172	114	0.196	128	0.220	142	0.242	156	0.265
101	0.175	115	0.198	129	0.221	143	0.243	157	0.267
102	0.177	116	0.201	130	0.222	144	0.245	158	0.269
103	0.178	117	0.202	131	0.224	145	0.248	159	0.271
104	0.179	118	0.203	132	0.226	146	0.250	160	0.273
105	0.180	119	0.205	133	0.228	147	0.251	161	0.274
106	0.183	120	0.206	134	0.230	148	0.252	162	0.275
107	0.185	121	0.207	135	0.231	149	0.253	163	0.278
108	0.187	122	0.209	136	0.232	150	0.256	164	0.279
109	0.188	123	0.211	137	0.235	151	0.257	165	0.280
110	0.192	124	0.213	138	0.236	152	0.258	166	0.282
111	0.193	125	0.214	139	0.237	153	0.261	167	0.284
112	0.193	126	0.215	140	0.239	154	0.262	168	0.285
113	0.194	127	0.218	141	0.241	155	0.264	169	0.287
								170	0.289

pression and the ratio of .44 Δ^t serum/Δ^t sodium in serum is approximately 1.00.

HYPONATREMIA ASSOCIATED WITH CHRONIC DISEASE. Table 4 lists 9 patients with various chronic illnesses who had a low serum sodium. Five of these patients had portal cirrhosis. As in the cases of dilution hyponatremia the sodium in the serum without any appreciable change in the freezing point depression of the serum. During treatment the ratio of .44 Δ^t serum/Δ^t sodium in serum tended to approach 1.00 and in 4 cases went below 1.10 with symptomatic improvement in the patients' condition. The fifth case (G.G.) was terminal and expired.

TABLE 2.—CONTRIBUTION OF SERUM SODIUM TO TOTAL FREEZING POINT DEPRESSION OF SERUM IN 25 NORMAL PERSONS

Patient	*Serum Na (mEq./L.)*	*Δt Serum °C.*	*Δt Sodium in Serum °C.*	*$\frac{\Delta t \text{ Na in Serum °C.}}{\Delta t \text{ Serum °C.}}$*	*$\frac{.44\ \Delta t \text{ Serum °C.}}{\Delta t \text{ Na Serum °C.}}$*
1	138	0.520	0.236	0.45	0.97
2	140	0.530	0.239	0.45	0.98
3	138	0.540	0.236	0.44	1.01
4	140	0.560	0.239	0.42	1.02
5	139	0.560	0.237	0.42	1.03
6	142	0.560	0.242	0.43	1.01
7	139	0.530	0.237	0.45	1.03
8	141	0.550	0.241	0.44	1.02
9	139	0.520	0.237	0.46	0.96
10	145	0.565	0.248	0.44	1.00
11	141	0.560	0.241	0.43	1.01
12	139	0.540	0.237	0.44	1.00
13	139	0.550	0.237	0.43	1.02
14	141	0.540	0.241	0.45	0.98
15	141	0.540	0.241	0.45	0.98
16	141	0.540	0.241	0.45	0.98
17	143	0.560	0.243	0.44	1.00
18	139	0.540	0.237	0.44	1.00
19	137	0.565	0.235	0.42	1.05
20	139	0.550	0.237	0.43	1.02
21	137	0.540	0.235	0.44	1.01
22	137	0.530	0.235	0.44	0.99
23	137	0.520	0.235	0.45	0.97
24	138	0.540	0.237	0.44	1.01
25	137	0.530	0.235	0.44	0.99

Mean = 0.439 Range = 0.42 to 0.46 S.D. = 0.024

freezing point of the serum is still contributing its expected 44% to the freezing point depression of the serum so that the ratio of .44 Δ^t serum/Δ^t sodium serum is approximately 1.00.

SODIUM DEPLETION. Table 5 illustrates 5 cases of true sodium depletion in patients who were severely ill. The ratio of .44 Δ^t serum/Δ^t sodium in serum is greater than 1.10. In each of these 5 cases the administration of 3% sodium chloride increased the concentration of

HYPONATREMIA WITH HYPERTONICITY. Table 6 shows 5 cases of low serum sodium associated with marked hypertonicity due to severely disturbed kidney function. All patients were uremic and four of them were in various stages of so-called "lower nephron nephrosis." One patient had uncontrolled diabetes. In this instance the serum sodium is low as in the examples cited above but the freezing point of the serum is markedly depressed indicating

TABLE 3.—DILUTION HYPONATREMIA

Patient	*Serum Na (mEq./L.)*	*$\triangle t$ Serum °C.*	*$\triangle t$ Na Serum °C.*	*$\frac{.44\ \triangle t\ Serum\ °C.}{\triangle t\ Na\ Serum\ °C.}$*	
M.L.	116	0.48	0.201	1.05	69-yr. old W/F following cataract surgery received 3 L. of 5% glucose in H_2O and 1 L. saline daily for 5 days. Patient recovered after limitation of fluids with final $\triangle t$ of 0.54° C. and serum Na of 136 mEq./L.
O.K.	116	0.44	0.201	0.96	Elderly W/M with cerebral arteriosclerosis. Received 3 L. of 5% glucose in H_2O daily for 9 days. Died on day of determinations due to congestive heart failure aggravated by overhydration.
J.Z.	125	0.51	0.214	1.05	96-yr. old W/M with cerebral thrombosis. Received 2000 ml. of 5% glucose in H_2O and 1000 ml. of H_2O by tube feeding with occasional additions of 5% glucose in saline for 8 days before determinations. Died of congestive heart failure aggravated by overhydration.
T.W.	123	0.50	0.211	1.04	88-yr. old W/F had transverse colostomy due to obstructing diverticulitis of colon. Average I.V. fluids amounted to 2000 ml. of 5% glucose in H_2O and 1000 ml. normal saline daily for 8 days prior to determinations. Recovered after limitation of fluids with final freezing pt. depression of 0.53° C. and serum Na of 135 mEq./L.
J.K.	115	0.47	0.198	1.04	69-yr. old W/M with generalized arteriosclerosis and pyelonephritis. Received 2000 ml. of 5% glucose in H_2O I.V. daily for 10 days prior to determinations and unknown quantity of fluids by mouth. I.V. fluids discontinued. 10 days later Na rose to 135 mEq./L., $\triangle t$ to .57° C.
A.P.	116	0.47	0.201	1.02	63-yr. old W/M. Post thoractomy status. Received average of 2000 ml. glucose in H_2O and 500 ml. normal saline I.V. plus 1000 ml. H_2O by stomach tube daily for 7 days before determinations. With limitation of fluids Na rose to 136 mEq./L. and $\triangle t$ to 0.54 in 8 days with recovery.

TABLE 4.—HYPONATREMIA ASSOCIATED WITH CHRONIC DISEASE
(? CHRONIC CELLULAR HYPO-OSMOLARITY)

Patient	*Serum Na (mEq./L.)*	*$\triangle t$ Serum (°C.)*	*$\triangle t$ Na Serum (°C.)*	*$\frac{.44\ \triangle t\ Serum}{\triangle t\ Na\ Serum}$*	*Diagnosis*
E.O.	126	0.50	0.215	1.02	Pulmonary TBC
G.F.	121	0.50	0.207	1.07	Portal cirrhosis
T.W.	123	0.50	0.211	1.04	Portal cirrhosis
M.R.	128	0.50	0.220	1.00	Ulcerative colitis with fatty stage of portal cirrhosis.
A.O.	126	0.49	0.215	1.00	Malnutrition, senility
A.M.	126	0.49	0.215	1.00	Portal cirrhosis
M.N.	126	0.49	0.215	1.00	Senility, pulmonary TBC
F.S.	117	0.47	0.202	1.02	Portal cirrhosis
G.R.	124	0.48	0.213	0.98	Portal cirrhosis

hypertonicity. The ratio of .44 Δ^t serum/Δ^t sodium in serum is greater than 1.10.

Discussion. By defining the serum sodium in relation to its contribution to the freezing point depression of the serum, four types of hyponatremia may be differentiated (Table 7). In all of these the serum sodium is low. However, the tonicity as measured by the freezing point of the serum is low in dilution hyponatremia (normal total extracellular sodium) and in chronic cellular hypo-osmolarity, is normal in salt depletion (decreased total extracellular sodium) and is high when the hyponatremia is associated with markedly impaired kidney function. Stated in another manner the equation of .44 Δ^t serum/Δ^t sodium in serum should equal 1.00 when the sodium is contributing its expected amount to the freezing point depression of the serum. In dilution hyponatremia and in chronic cellular hypo-osmolarity, although the tonicity of the serum is low, the sodium is contributing its expected amount and the equation .44 Δ^t serum/Δ^t sodium in serum = 1.00 $\pm$ 0.10. In salt depletion although the

TABLE 5.—SODIUM DEPLETION

Patient	*Serum Na (mEq./L.)*	*NPN (mg./100 ml.)*	*Δt Serum °C.*	*Δt Na Serum °C.*	*.44 Δt Serum / Δt Na Serum*	
M.R.	124	87	0.53	0.213	1.10	Patient had salt-losing phase of chronic glomerulonephritis. 3% NaCl administered I.V. with restriction of fluids resulted in raising Na to 132 mEq. and ratio to 1.05. Died 7 mos. later of uremia due to chronic glomerulonephritis.
F.C.	124	60	0.565	0.213	1.16	Patient had salt depletion syndrome from excess sweating during very hot weather with free access to H_2O. Given 3% NaCl with restriction of H_2O resulting in elevation of Na to 140 mEq. and decreased the ratio to 1.04 with recovery.
E.K.	119	35	0.54	0.205	1.15	Patient had metastatic carcinoma of stomach to liver and peritoneum. Developed ascites and became salt depleted following paracentesis. Given 3% NaCl I.V. with restriction of fluids resulting in increase of Na to 128 and ratio to 1.09 with symptomatic recovery. Died one week later from metastatic carcinoma.
W.S.	123	35	0.54	0.211	1.13	Patient with vomiting 2 days before sodium determination. Vomiting stopped and patient was treated over 2 days with 1 L. of saline per day. At that time the sodium was 139 mEq. and Δt serum 0.52 with ratio of 0.97.
G.C.	107	28	0.50	0.185	1.19	51-yr. old W/F, cirrhotic. Developed weakness, hypotension, mental confusion, which proceeded to coma 2 days after abdominal paracentesis. Patient died in spite of I.V. administration of 3% NaCl with rise in serum sodium to 111 mEq. and reduction of ratio to 1.14.

sodium is low the tonicity of the serum is near normal and the equation of .44 Δ^t serum/Δ^t sodium in serum is greater than 1.10. On hyponatremia associated with severely disturbed kidney function the sodium may be low and tonicity as measured by the freezing point depression is markedly elevated so that the ratio .44 Δ^t serum/Δ^t sodium in serum is greater than 1.10.

In many instances a careful history and physical examination will indicate the genesis of the hyponatremia; in other instances the cause will remain obscure. Both chronic cellular hypo-osmolarity and dilution hyponatremia have a low sodium and a low tonicity as measured by the freezing point depression. These cannot be separated by applying the above method. However, in chronic cellular hypo-osmolarity there is no history of the patient having had large amounts of intravenous fluids and these patients are often malnourished and chronically ill. In patients with dilution hyponatremia there is usually a history of the patient having received large amounts of electrolyte-free fluids.

The greatest difficulty occurs in differentiating hyponatremia due to dilution (normal total extracellular so-

TABLE 6.—HYPONATREMIA ASSOCIATED WITH HYPERTONICITY

Patient	*Serum Na* (*mEq./L.*)	Δt *Serum* °C.	Δt *Na Serum* °C.	$\frac{.44\ \Delta t\ Serum}{\Delta t\ Na\ Serum}$	
F.W.	125	0.625	0.214	1.28	Lower nephron nephrosis. Died following artificial dialysis with Kolff Kidney.
T.B.	129	0.69	0.221	1.32	Lower nephron nephrosis, died on fifth anuric day.
C.R.	125	0.60	0.214	1.23	Lower nephron nephrosis, recovered.
J.S.	129	0.61	0.221	1.21	Uncontrolled diabetes, nephrosclerosis, mild uremia. Myocardial infarct. Improved with diabetic control.
J.L.	120	0.59	0.206	1.26	Lower nephron nephrosis following shock associated with acute hemorrhagic pancreatitis. Recovered on conservative treatment.

TABLE 7.—CLINICAL TYPES OF HYPONATREMIA AND THE RELATIONSHIP OF SERUM SODIUM TO TOTAL SERUM TONICITY.

	Serum Na	*Tonicity* (*As Measured by* Δt *Serum*)	$\frac{.44\ \Delta t\ Serum}{\Delta t\ Na\ Serum}$ = (*Contribution of Serum Na to* Δt *of Serum*)
Normals	Normal	Normal	0.96 – 1.05
Dilution Hyponatremia	Low	Low	0.96 – 1.10
Chronic Cellular Hypo-osmolarity	Low	Low	0.96 – 1.10
Salt Depletion	Low	Normal	>1.10
Hyponatremia with Hyperosmolarity	Low	High	>1.10

dium) from hyponatremia due to sodium loss (low total extracellular sodium). It is frequently stated that these two states often occur together and this may well be the case. However, these data suggest that true salt depletion can be differentiated from dilution hyponatremia by the simple expedient of defining the serum sodium in relationship to its contribution to the total tonicity of the serum as measured by the freezing point depression. In those cases of hyponatremia due to dilution the freezing point depression should be decreased while the sodium maintains its expected 44% contribution to the freezing point depression of the serum. In hyponatremia due to true salt loss the freezing point depression of the serum is in the normal range and the sodium does not contribute its expected 44% to the freezing point depression of the serum. The factors maintaining the serum tonicity at normal levels during sodium depletion are speculative (Rubin *et al.*[4]). The normal or moderate elevation of the nonprotein nitrogen in the patients with sodium depletion excludes this factor as maintaining the tonicity. Concentrations of solutes other than sodium by water depletion might be a factor in maintaining normal serum osmolarity in the presence of sodium depletion.

Hyponatremia associated with marked derangement of kidney function is usually determined from the history of severe renal disease and by a simple urinalysis. Since it has been shown that the hyponatremia in these instances may be due in part to intracellular sodium shift (Iseri *et al.*[3], Rubin *et al.*[4], and Serota and Kroop[5]) or to overhydration with dilution of electrolytes (Elkinton and Danowski[1]), the total body sodium tends to be near normal and replacement of the sodium by intravenous fluids is not necessary, and, in fact, is hazardous. In these instances the finding of hypertonicity as measured by marked depression in the freezing point of the serum and a hyponatremia in which the sodium does not contribute its expected 44% of the serum freezing point should confirm this diagnosis which has been made clinically.

We have used this method in over 100 cases of low serum sodium determinations and have found it a helpful laboratory adjunct to the diagnosis and management of hyponatremic states.

Summary and Conclusions. 1. A method is described whereby the contribution of the serum sodium to the total freezing point depression of the serum can be measured.

2. It was demonstrated in normal individuals that sodium contributes approximately 44% to the freezing point depression of any given specimen of serum or that .44 Δ^t serum/Δ^t sodium of serum $= 1.00 \pm 0.10$.

3. In dilution hyponatremia and in chronic cellular hypo-osmolarity the Δ^t of the serum is raised but the sodium continues to contribute its expected 44% to the Δ^t of the serum.

In true sodium depletion the Δ^t of the serum is within the normal range but the sodium contributes less than 44% to the Δ^t of the serum.

5. In advanced kidney disease there may be a low serum sodium but a marked increase in the tonicity of the serum as measured by the freezing point depression. In this instance the sodium does not make up its expected 44% to the contribution to the freezing point depression.

6. It is suggested that by expressing the serum sodium in terms of its contribution to the freezing point depression of that specimen of serum a laboratory guide is available to elucidate hyponatremic states and to initiate proper therapy.

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SUMMARIO IN INTERLINGUA

Le Relation Inter le Natrium del Sero e le Osmolaritate Total del Sero: Un Methodo pro Distinguer Statos Hyponatremic

1. Es describite un methodo que permitte mesurar le contribution del natrium seral al depression total del puncto de congelation del sero.

2. Esseva demonstrate in individuos normal que le natrium del sero contribue circa 44% al depression total del puncto de congelation de un specimen particular de sero. Alteremente exprimite, 0,44 Δ^t del sero dividite per Δ^t del natrium seral $= 1{,}00 \pm 0{,}10$.

3. In hyponatremia a dilution e in chronic hypo-osmolaritate cellular, le Δ^t del sero es elevate, sed le natrium continua contribuer le expectate 44% al Δ^t del sero.

4. In ver depletion del natrium, le Δ^t del sero se tene intra limites normal, sed le natrium contribue minus que 44% al Δ^t del sero.

5. In avantiate morbo renal, il pote occurrer un basse nivello de natrium seral, sed isto es accompaniate per un marcate augmento del tonicitate seral manifeste in mesurationes del depression del puncto de congelation. In iste situation, le natrium non contribue su expectate 44% al total depression del puncto de congelation.

6. Es suggerite que per exprimer le natrium de un specimen de sero per le valor de su contribution al total depression del puncto de congelation de ille specimen de sero, on se procura un guida laboratorial in clarificar statos de hyponatremia e in initiar le correspondente therapia.

SERUM TRANSAMINASE ACTIVITY:

A COMPARISON OF THE PYRUVIC AND OXALACETIC TRANSAMINASES*

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Since the initial report of LaDue, Wroblewski and Karmen[7] on the striking transient elevation of serum glutamic-oxalacetic transaminase activity in acute myocardial infarction, considerable interest has been aroused in the serum glutamic-oxalacetic transaminase level as a diagnostic aid. Subsequent investigations revealed that elevations in serum glutamic-oxalacetic transaminase activity, henceforth referred to as oxalacetic transaminase, were not restricted to myocardial necrosis (Rudolph, Dutton and Schaefer[8], and Wroblewski and LaDue[11]).

More recent reports have attempted to clarify the significance of abnormalities in serum oxalacetic transaminase activity in relation to disease states (Chinsky *et al.*[1,2]). It is apparent that an elevated serum oxalacetic transaminase level is not specific for a particular disease state but must be carefully interpreted in relation to a number of factors which may contribute to the serum transaminase activity. Despite the lack of specificity for a particular disease state, the oxalacetic transaminase assay, when properly interpreted, has proven to be a very valuable adjunct to clinical diagnosis.

As a result of the observations on the oxalacetic transaminase, several investigators have studied other serum enzymes which might prove more useful as a clinical diagnostic aid in determining the presence of active tissue necrosis. These include lactic dehydrogenase (Hsieh and Blumenthal[5], White[10], and Wroblewski and LaDue[11]), aldolase (Volk *et al.*[9]), and glutamic-pyruvic transaminase (De Ritis, Coltorti and Guisti[3,4], and Wroblewski and LaDue[13]). The latter, henceforth referred to as pyruvic transaminase, is said to be more sensitive than the oxalacetic transaminase in depicting acute hepatocellular damage, and less sensitive as an indicator of acute myocardial necrosis (Wroblewski and LaDue[13]). The relative differences in serum enzyme concentrations in these latter conditions is said to correlate with the observed differ-

*These studies were supported by a grant from the St. Louis Heart Association.

ences in enzyme concentration of the tissues involved (Wroblewski and LaDue[13]).

It is the purpose of this report to compare the oxalacetic transaminase activity to the pyruvic transaminase activity in the sera of 150 patients with a variety of diseases and to discuss the value of the pyruvic transaminase assay as a diagnostic aid.

Methods. Serum oxalacetic transaminase activity was assayed by the method of Karmen[6]. By substituting alanine for aspartate, and lactic dehydrogenase for malic dehydrogenase, the Karmen method as modified by Wroblewski and LaDue[13] was utilized for assaying pyruvic transaminase. In either assay, one transaminase unit has been defined as that amount of enzyme which will cause a unit drop in optical density per minute under the conditions of the test.

Serum obtained from clotted blood specimens was assayed for both oxalacetic and pyruvic transaminase levels. It was observed that the pyruvic transaminase in serum has approximately the same order of stability as the oxalacetic transaminase (Chinsky and Sherry[1]). As with oxalacetic transaminase, the pyruvic transaminase assay does not require additional pyridoxal phosphate, is not influenced by the presence of anticoagulants, but is significantly increased in the presence of hemolysis.

The literature (Chinsky and Sherry[1], and Wroblewski and LaDue[11]) indicates that the normal range for serum oxalacetic transaminase is 5 to 40 units/ml. (Av. 22 ± 7). The normal serum pyruvic transaminase ranges from 5 to 30 units/ml. (Av. 16 ± 9)* (Wroblewski and LaDue[13]) or somewhat lower than the oxalacetic transaminase. The following arbitrary definition of ranges of serum activity for these two enzymes was made as follows:

	Oxalacetic Transaminase Units per ml. of Serum	*Pyruvic Transaminase Units per ml. of Serum*
Normal	up to 40	up to 30
Borderline	41 to 50	31 to 40
High	above 50	above 40

In comparing the oxalacetic to the pyruvic transaminase in patients we have considered a ratio of approximately 1.25 to 1.0 as being a normal ratio.

As a background for some of the observations to be reported, the effect of common duct ligation on the serum pyruvic and oxalacetic transaminase in the rat was studied. For this experiment, 12 normal rats were divided into two groups of 6 animals. The animals in one group were subjected to common duct ligation while the animals in the other group were sham operated and acted as controls.† Blood specimens were collected just prior to surgery, and at 3 hours, 6 hours, 24 hours, and 6 days following surgery. The sera were assayed for both pyruvic and oxalacetic transaminase. The animals were sacrificed at the end of the experiment. At this time the duct ligated group were all intensely icteric, and were observed to have widely dilated and distended common ducts. However, no evidence of hepatic necrosis was seen on histological examination.‡

The results of the serum enzyme assay are shown in Fig. 1.

As can be seen from the data in Fig. 1 the serum pyruvic and oxalacetic transaminase activities of the sham operated controls did not significantly change during the entire period of observation. In contrast, ligation of the common duct was shortly followed by a sharp rise in the serum levels of both transaminases. The oxalacetic transaminase was increased to a much greater degree than the pyruvic transaminase. Both enzyme activities reached a peak 6 hours after duct ligation and then began to recede despite continuation of the obstruction. By the 6th postoperative day the pyruvic transaminase level had almost reached to a normal level whereas the oxalacetic transaminase was still considerably elevated.

Results. For the purposes of presentation, the 150 patients which comprise this study will be discussed under three major categories: patients with cardiac diseases; patients with hepatic, biliary and metastatic malignant diseases; and patients with miscellaneous diseases. Although multiple or serial determinations were obtained in most

*In our own series of 16 normal individuals, the serum pyruvic transaminase assays all fell within the normal range described above.

†We are indebted to Dr. Stanley Lang for carrying out the surgical procedures.

‡We are indebted to Dr. H. T. Blumenthal for these observations. In a previous study, no histological evidence of hepatic necrosis was evident 24 hours after ligation (Chinsky and Sherry[1]).

instances, the highest of each of the transaminase activities observed, will be used in discussing the results.

PATIENTS WITH CARDIAC DISEASES. In Fig. 2 is shown a comparison of the serum oxalacetic to the serum pyruvic transaminase level in 50 cardiac patients.

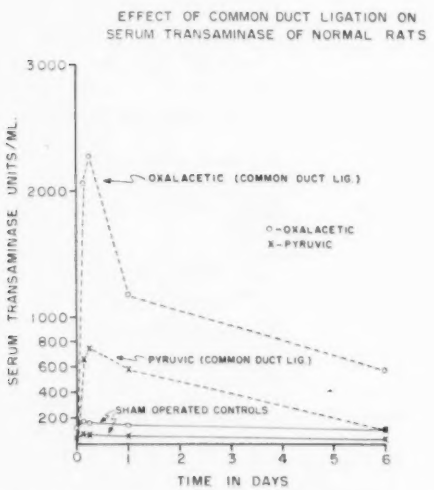

Fig. 1.—Effect of common duct ligation on serum oxalacetic and pyruvic transaminase levels of normal rats. See text for details.

Included among the latter are 24 patients with acute myocardial infarction, 14 with the anginal syndrome, 7 with congestive heart failure, 3 with cardiac arrhythmias, and one each with pulmonary edema, and rheumatic heart disease immediately after catheterization. The values observed in the patients with myocardial infarcts are shown in Fig. 2 as solid dots, whereas the levels in the other cardiac patients are referred to by crosses. The diagonal line bisecting Fig. 2 represents a ratio of oxalacetic to pyruvic transaminase activity of 1.25 to 1. Equal increases in the two transaminase activities would be expected to fall along this line. On the other hand, proportionately greater increases in oxalacetic transaminase would be represented by points falling to the left of the diagonal line, and proportionately greater increases in the pyruvic transaminase would be represented by falling to the right of the diagonal line. In

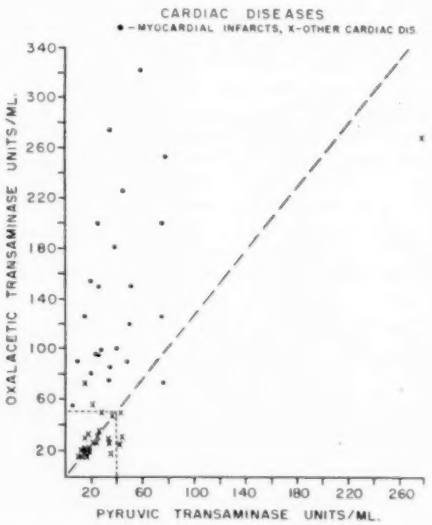

Fig. 2.—Comparison of the serum oxalacetic and pyruvic transaminase levels in 50 patients with cardiac diseases. Broken diagonal line represents the normal oxalacetic to pyruvic transaminase ratio of 1.25 to 1.0. In the lower left hand corner the upper limits of the normal range for each of the transaminase levels is shown by an interrupted line. See text for details.

the lower left hand corner of Fig. 2, the upper limits of normal for each of the two assays are indicated by a broken line.

From the data in Fig. 2 it will be seen that all the patients with acute myocardial infarctions developed elevated oxalacetic transaminase levels, while only 9 of the 24 patients developed an elevated pyruvic transaminase. With one exception, the rise in oxalacetic transaminase was consid-

erably greater than the rise in pyruvic transaminase. This disparity in increase between the two transaminases is illustrated by the data in Fig. 3, which depicts the serial changes in serum oxalacetic and pyruvic transaminase occurring in a patient with an acute myocardial infarction.

As seen in Fig. 3, although there is some increase in the serum pyruvic transaminase following an acute myocardial infarction, the changes are relatively insignificant when compared to the striking increases observed in the oxalacetic transaminase. Since the myocardium is approximately twenty times richer in oxalacetic as compared to pyruvic transaminase (Wroblewski and LaDue[13]), the observations in the patients with acute myocardial infarction are consistent with the differences in myocardial concentration of the two enzymes.

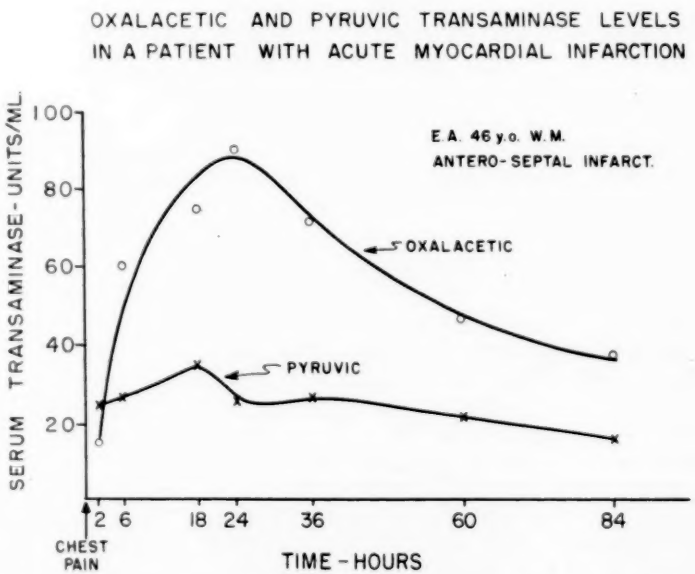

Fig. 3.—Serial serum oxalacetic and pyruvic transaminase levels in a patient with an acute myocardial infarction. The abscissa represents time in hours following the onset of severe chest pain.

Six of the 26 cardiac patients who did not have evidence of acute myocardial infarction had either an elevated serum oxalacetic or serum pyruvic transaminase. In two instances the oxalacetic transaminase alone was elevated (72, 56 units/ml.), in 3 instances the serum pyruvic transaminase alone was elevated (42, 44, 43 units/ml.), and in one patient both transaminases were elevated (oxalacetic 270; pyruvic 275 units/ml.). Of the 2 patients with elevations restricted to the serum oxalacetic transaminase, one had a rapid cardiac arrhythmia (atrial fibrillation) and the other was a rheumatic cardiac who had been subjected to right heart catheterization. The 3 patients with elevations restricted to the serum pyruvic transaminase were suffering from congestive heart failure secondary to degenerative heart disease. The lone patient who demon-

strated a striking increase in both the serum oxalacetic and pyruvic transaminase was an arteriosclerotic cardiac who presented with a rapid ventricular tachycardia and expired shortly thereafter. Postmortem examination revealed marked centrilobular liver cell necrosis.

Comment on patients with cardiac diseases. The observations cited above, confirm the observations of Wroblewski and LaDue that the serum oxalacetic transaminase is much more strikingly elevated than the pyruvic transaminase in patients with acute myocardial infarctions and, when both assays are simultaneously performed, may serve to differentiate acute myocardial infarction from hepatic necrosis (Wroblewski and LaDue[13]). Nevertheless it is also evident that in a significant number of patients with acute myocardial infarction, the serum pyruvic transaminase does become elevated during the course of the disease. From the studies of Wroblewski and LaDue[13] it is apparent that other tissues, for example, skeletal muscle, pancreas, spleen and lung are much richer in oxalacetic as compared to pyruvic transaminase, and extensive necrosis of these latter organs may lead to changes similar to those described for acute myocardial infarction.

It is interesting to note that 3 of the 7 patients with congestive failure revealed mild elevations in pyruvic transaminase alone, suggesting a possible relationship to chronic passive congestion of the liver.

The observation of elevated oxalacetic transaminase in rapid arrhythmias has been previously commented upon (Chinsky *et al.* [1,2]). We have suggested that this elevation may be due to centrilobular liver cell necrosis secondary to a diminished cardiac output. This view receives additional support from the observations on the patient with the rapid ventricular tachycardia who subsequently expired. Both the pyruvic and oxalacetic transaminases were elevated, and necropsy revealed extensive liver cell necrosis.

PATIENTS WITH HEPATIC, BILIARY TRACT, AND METASTATIC MALIGNANT DISEASES. Figure 4 summarizes our observations on 35 patients with hepatic or biliary tract disease, and on 15 patients with metastatic malignant disease.

Included among the cases of hepatic and biliary tract disease studied were 5 patients with viral hepatitis, 15 with cirrhosis of the liver, 5 with common duct obstruction secondary to lithiasis, 4 with "Thorazine" jaundice, 4 with acute interstitial pancreatitis associated with biliary tract disease, and single instances of subhepatic abscess, and marked centrilobular liver cell necrosis. The latter diagnosis was established at postmortem examination in a patient with idiopathic cardiac hypertrophy with intractable congestive failure who became icteric shortly before his demise.

As can be seen in Fig. 4, four of the 5 patients with hepatitis had a significantly higher serum pyruvic transaminase level than oxalacetic transaminase level. In one patient the reverse was observed. The highest levels of transaminase activity were observed in patients during the initial phase of viral hepatitis.

Whereas 10 of the 15 patients with cirrhosis of the liver had elevated oxalacetic transaminases, only 6 demonstrated an elevated pyruvic transaminase. In 4 instances both transaminase levels were in normal range. It is of interest that of the 4 patients with normal oxalacetic and pyruvic transaminases, one was in hepatic coma. In another instance of hepatic coma, the pyruvic transaminase was normal (33 units), but the oxalacetic transaminase

was elevated (100 units). Necropsy showed little evidence of hepatic necrosis. In contrast to the patients with viral hepatitis, when the transaminase levels were elevated in patients with cirrhosis of the liver, the oxalacetic transaminase was usually more elevated than the pyruvic transaminase.

Of the 5 patients with extrahepatic obstructive jaundice secondary to lithiasis, 3 demonstrated an elevated oxalacetic transaminase while 4 had an elevated pyruvic transaminase. Although there was a slight tendency for the pyruvic transaminase to be elevated to a greater extent than the oxalacetic transaminase, this discrepancy was not as pronounced as in the patients with acute hepatitis. However, it is apparent that the observations were limited to a small number of patients with either condition.

The observations on the 4 patients with intrahepatic obstruction secondary to Thorazine sensitivity followed the same pattern as the hepatitis cases, although the transaminase levels were not as strikingly elevated. Three of the 4 patients had considerable elevations in their pyruvic transaminase levels, while the fourth was only moderately elevated. In contrast, 3 demonstrated only moderate elevations in the oxalacetic transaminase, and one patient had a normal level.

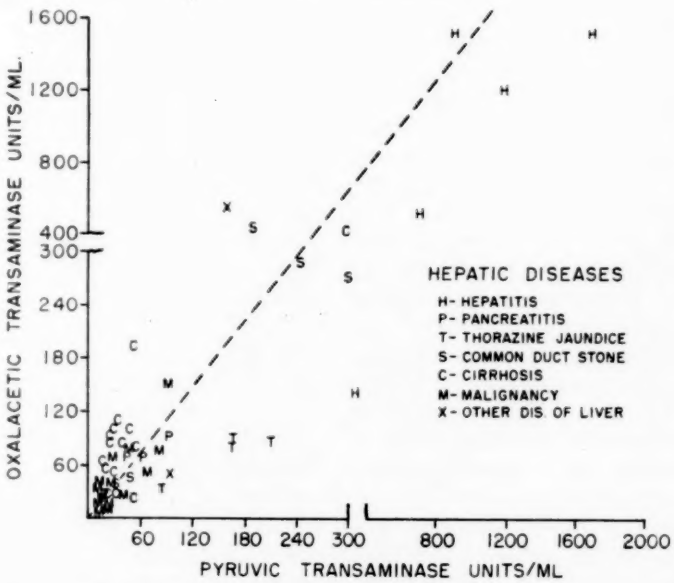

Fig. 4.—Comparison of the serum oxalacetic and pyruvic transaminase levels in 50 patients with hepatic diseases. See text for details.

All 4 patients with "acute interstitial pancreatitis" associated with biliary tract disease had serum amylase levels of several thousand units per milliliter, and 3 of these patients had elevations in both the serum oxalacetic and pyruvic transaminases. The observed values fell along the projected line of a normal serum ratio for the two transaminases.

In the two instances referred to in Fig. 4 as other diseases of the liver, the patient with a subhepatic abscess

had a distinctly elevated pyruvic transaminase level but an oxalacetic transaminase level at the upper limits of normal (pyruvic transaminase 95 units, oxalacetic transaminase 50 units), while the patient with extensive centrilobular liver cell necrosis had large increases in the levels of both transaminases (pyruvic transaminase 170 units, oxalacetic transaminase 450 units).

Among the 15 patients with metastatic malignant disease, 5 had proven hepatic metastases either by biopsy, laparotomy or necropsy. Four of this latter group had elevated pyruvic and oxalacetic transaminase levels while the fifth had an elevated oxalacetic transaminase level only. In general the ratio of both transaminases was close to the normal. In the 10 patients in whom hepatic metastases could not be established, both transaminase activities were in the normal range.

Comment on patients with hepatic, biliary tree, and metastatic malignant diseases. Hepatic tissue in contrast to cardiac and skeletal muscle is rich in both oxalacetic and pyruvic transaminases with the former being present in somewhat higher concentration (Wroblewski and LaDue[13]). In viral hepatitis, both experimental (De Ritis, Coltorti and Guisti[4]) and clinical (De Ritis, Coltorti and Guisti[3], and Wroblewski and LaDue[13]) it has been demonstrated that the serum pyruvic transaminase rises to higher levels than the serum oxalacetic transaminase. As a result, it has been suggested that the serum pyruvic transaminase appears to be a more sensitive indicator than the oxalacetic transaminase in depicting acute hepatocellular damage.

Although our studies confirm the earlier clinical observations of Wroblewski and LaDue[13], and of De Ritis *et al.*[3] it would appear that the serum pyruvic transaminase is not uniformly more sensitive than the oxalacetic transaminase as an indicator of hepatocellular damage (see patients with cirrhosis of the liver), nor is it more specific for hepatocellular damage (see patients with Thorazine jaundice). The serum pyruvic transaminase appears to be elevated in the same diseases of the liver and biliary tract

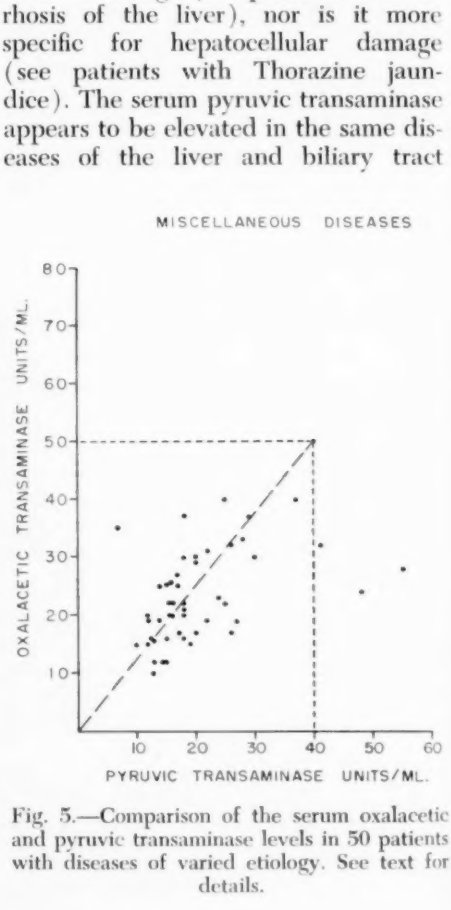

Fig. 5.—Comparison of the serum oxalacetic and pyruvic transaminase levels in 50 patients with diseases of varied etiology. See text for details.

which influence the serum oxalacetic transaminase (Chinsky and Sherry[1]). The relative differences in elevation of the serum levels of the two enzymes observed in the conditions described, appear to result from factors which are not as yet apparent and require further investigation.

PATIENTS WITH MISCELLANEOUS DISEASES. Fifty patients with a variety of miscellaneous diseases of infectious, inflammatory, metabolic, and degenerative nature were studied. The results

are shown in Fig. 5. In 47 of the patients both the serum oxalacetic and pyruvic transaminase levels were in the normal range. Included among these cases were the following: bronchopneumonia (4); cerebral vascular accidents (4); convulsive disorder (3); psychoneurosis (3); acute cholecystitis (2) chronic uremia (2); chronic nephritis without uremia (2); duodenal ulcer (2); rheumatoid arthritis (2); upper respiratory infection (2); diabetes mellitus (1); benign hypertension (1); hyperthyroidism (1); ruptured ovarian follicle (1); ulcerative colitis (1); spastic colitis (1); decubitus ulcer (1); severe malnutrition (1); nasal hemorrhage (1); heat exhaustion (1); polycythemia vera (1); gastric ulcer (1); myotonia atrophica (1); hemolytic anemia (1); neurodermatitis (1); iron deficiency anemia (1); mesenteric adenitis (1); acute rheumatic fever (1); osteomyelitis (1); aneurysm of abdominal aorta (1); and multiple renal calculi (1).

In the other 3 patients, the serum oxalacetic transaminase assay was normal but the serum pyruvic transaminase was slightly elevated as follows: asthma with bronchopneumonia (55 units), diabetic acidosis (41 units), and acute hypertensive encephalopathy (48 units). The mechanism for the elevated pyruvic transaminase in these latter patients is not apparent. It may be noted that renal insufficiency *per se* did not elevate either the serum pyruvic or oxalacetic transaminase level.

Discussion. Stimulated by the observations on serum glutamic-oxalacetic transaminase, studies are being conducted to determine whether the serum level of other enzymes might prove more useful or specific in determining the presence of active tissue necrosis. From the observations cited in this report, it is apparent that the serum pyruvic transaminase assay *by itself*, although more specific for hepatic disease as compared to myocardial necrosis, is neither specific for hepatic necrosis nor necessarily more sensitive than oxalacetic transaminase as an index of hepatic injury. At present, because of the large number of diseases which may elevate the serum oxalacetic transaminase level, the assay of this latter enzyme when carried out at the appropriate time, has proven most useful in excluding the presence of significant myocardial or hepatic necrosis. Our observations suggest that as a general diagnostic aid, the pyruvic transaminase assay would prove most useful in even a more limited area, that is, in excluding the presence of hepatic necrosis. On the other hand, the simultaneous determination of both enzyme levels may be expected to yield additional information as to the type of organ or mechanism which may be involved in elevating the serum oxalacetic transaminase level.

Summary and Conclusions. 1. The serum glutamic-oxalacetic and glutamic-pyruvic transaminase activities were determined in 150 patients with a variety of diseases.

2. Almost all patients with acute myocardial infarction developed a much more significant elevation in the oxalacetic transaminase than in the pyruvic transaminase. While an elevation in the serum oxalacetic transaminase was a consistent finding in patients with acute myocardial infarction, the serum pyruvic transaminase was elevated in some, and normal in others.

3. Elevations in the serum levels of both transaminase enzymes were observed in patients with a variety of hepatic diseases (hepatitis, cirrhosis, centrilobular liver cell necrosis, and metastatic malignancy to the liver), intra- and extrahepatic biliary obstruc-

tion, and in acute interstitial pancreatitis. Although patients with viral hepatitis usually demonstrated higher levels of serum pyruvic as compared to serum oxalacetic transaminase, the serum pyruvic transaminase level was not observed to be either a uniformly more sensitive or a more specific indicator of hepatic necrosis.

4. At the present state of knowledge, the pyruvic transaminase assay should find its greatest use as an adjunct in the interpretation of an elevated oxalacetic transaminase level.

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SUMMARIO IN INTERLINGUA

Activitate de Transaminase Seral: Un Comparation del Transaminases Pyruvic e Oxalacetic

1. Le activitate del transaminases glutamic-oxalacetic e glutamic-pyruvic del sero esseva determinate in 150 patientes con un varietate de morbos.

2. Quasi omne le patientes con acute infarcimento myocardial disveloppava multo plus significative elevationes del transaminase oxalacetic que del transaminase pyruvic. Durante que un elevation del transaminase oxalacetic del sero esseva un constatation regular in patientes con acute infarcimento myocardial, le transaminase pyruvic esseva elevate in certes de iste patientes e normal in alteres.

3. Elevationes del nivellos de ambe transaminases esseva observate in patientes con varie morbos hepatic (hepatitis, cirrhosis, necrosis de cellulas centrilobular, e malignitates con metastase al hepate), obstruction biliari intra- e extrahepatic, e acute pancreatitis interstitial. Ben que patientes con hepatitis viral exhibiva generalmente plus alte nivellos seral de transaminase pyruvic que de transaminase oxalacetic, il non esseva possibile concluder que le nivello seral de transaminase pyruvic es regularmente plus sensibile o plus specific como indicator de necrosis hepatic.

4. Sub le conditiones del stato presente de nostre cognoscentias, le test del transaminase pyruvic ha su plus grande utilitate como adjuncto in le interpretation de elevate nivellos de transaminase oxalacetic.

METHOXAMINE: EFFECT ON BLOOD PRESSURE AND RENAL HEMODYNAMICS*

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Methoxamine,† β-hydroxy-β(2,5 dimethoxyphenyl)-isopropylamine hydrochloride, is one of the newer, relatively long acting sympathicomimetic amines. Its prolonged action in raising blood pressure after a single intramuscular injection (King and Dripps[4], and Poe[10]) suggested that it might be a valuable drug in the treatment of hypotensive emergencies provided that no detrimental circulatory effects were associated with its administration. Since a decrease in renal function is a common accompaniment of the hypotensive state, it seemed desirable to test the effect of methoxamine on renal hemodynamics in normotensive human subjects. In addition, similar studies had been done previously with norepinephrine (Mills, Moyer and Skelton[7]) and Aramine (Livesay, Moyer and Chapman[5]), and it was desired to compare the effect of these three drugs on renal function. This was of particular interest since the previous data had shown that there might be some disproportion between the amount of renal vasoconstriction in relation to the amount of generalized vasoconstriction produced by these agents.

Methods. Seven normotensive, convalescent patients were studied. Renal clearances were performed by standard techniques and have been described elsewhere (Moyer and Mills[9]). Mean blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure, with the exception that in one subject it was measured directly by means of an indwelling arterial needle connected to a mercury manometer.

Following three to four consecutive 10-minute control periods, an infusion containing 120 mg. of methoxamine per liter was started intravenously. The rate was gradually increased over a 10- to 20-minute period until the desired blood pressure response had been obtained. At this time renal clearances were again measured during two to four consecutive 10-minute periods. Atropine was subsequently administered to 2 patients in a dose of 1 mg. intravenously to determine the effects on blood pressure and pulse rate.

Results. The effects of methoxamine on blood pressure and pulse rate are presented in Table 1. The average dose of the drug was 13.9 mcg./kg./min. This produced an average increase in mean blood pressure of 136% ($P < 0.001$), control pressure being represented as 100%. Systolic blood pressure, however, increased more than diastolic pressure, resulting in a rise in pulse pressure; concurrently there was a de-

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†Vasoxyl T.M.—Supplied through the courtesy of Burroughs-Wellcome & Co., Tuckahoe, N.Y.

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TABLE 1.—EFFECT OF METHOXAMINE ON BLOOD PRESSURE AND PULSE RATE

	Blood Pressure									Pulse Rate			Dose of Methoxamine
	Control			*Methoxamine*			*Atropine*						
Patient	*Sys.*	*Dias.*	*MBP.*	*Sys.*	*Dias.*	*MBP.*	*Sys.*	*Dias.*	*MBP.*	*C*	*M*	*A*	*mcg./kg./min.*
1	122	81	95	170	99	123	191	120	144	72	57	122	18.8
2	106	73	84	169	102	124	190	140	157	81	48	105	16.9
3	130	90	103	181	114	136	—	—	—	77	48		9.1
4	111	82	91	176	98	124	—	—	—	98	55		19.7
5	—	—	71*	—	—	114*	—	—	—	92	72		16.1
6	112	86	95	156	103	121	—	—	—	77	46		9.6
7	136	74	94	158	88	111	—	—	—	75	66		6.8
Mean Values	120	81	90	168	101	122				82	56		13.9
P Value†						<0.001					<0.01		

Key to Abbreviations:
Sys. = Systolic
Dias. = Diastolic
MBP. = Calculated mean blood pressure
C = Control
M = Methoxamine
A = Atropine
* True mean blood pressure

† P value derived from $t = \bar{x}\sqrt{\frac{n(n-1)}{S_x^2}}$

Statistical analysis by R. A. Seibert, Ph.D.

crease in pulse rate ($P<0.01$). Following administration of atropine to two subjects (Patients 1 and 2) there was a further rise in blood pressure, associated with tachycardia, suggesting that the preceeding bradycardia was a result of increased vagal activity (Table 1 and Fig. 1).

depression of the S–T segments over the left ventricle (Fig. 2), associated with the further rise in blood pressure after adminstration of atropine.

During administration of methoxamine, there was a significant ($P<0.01$) and often marked decrease in glomerular filtration rate (GFR) in most of

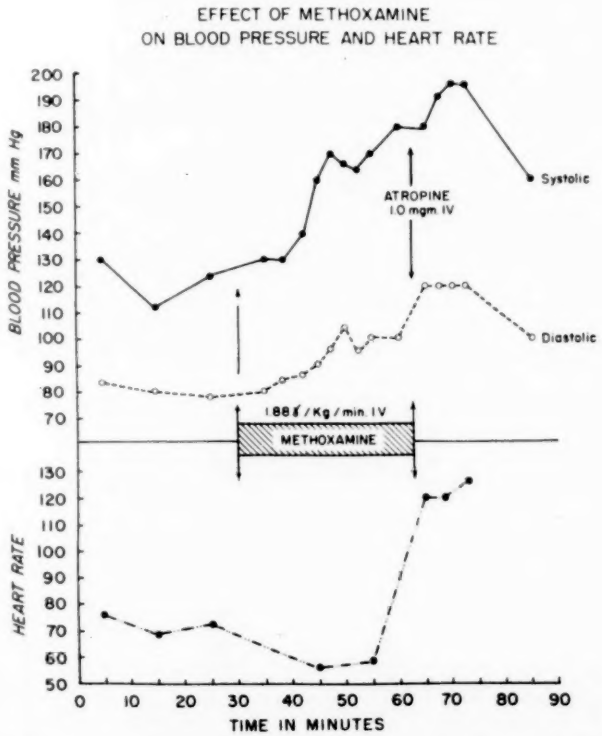

Fig. 1.—Typical blood pressure response during intravenous infusion of methoxamine. Note fall in pulse rate. Following administration of atropine there was further rise in blood pressure and increased pulse rate.

Electrocardiograms using leads 1, 2, 3, aVr, aVl, and aVf were taken during control and drug periods in each of the patients. Aside from the decrease in heart rate and associated increase in the P–R interval no significant changes were noted as a result of methoxamine administration. However, in one patient (Case 1), there was a significant

the patients (Table 2), the average value being 63% of the control level. However, in two patients (Cases 3 and 6) there was only a minimal fall in GFR. Renal plasma flow (RPF) was also depressed averaging 67% of the control which was statistically significant ($P<0.05$); however, in two patients (Cases 3 and 7) RPF was not

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TABLE 2.—EFFECT OF METHOXAMINE ON GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW

	*GFR*in			*FF*			*RPF*			*MBP*			*RBF*			*RVR*			*Dose*
Patient	*C*	*M*	%	*C*	*M*	%	*C*	*M*	%	*C*	*M*	%	*C*	*M*	%	*C*	*M*	%	*mcg./kg./min.*
1	133	56	42	.190	.136	72	701	413	59	95	123	129	1189	700	59	.080	.174	217	18.8
2	103	85	83	.157	.175	111	657	485	74	84	124	148	1113	808	73	.075	.153	204	16.9
3	127	112	88	.184	.170	92	691	663	96	103	136	132	1303	1205	92	.079	.113	143	9.1
4	119	64	54	.199	.189	95	599	338	56	91	124	136	986	489	50	.092	.254	276	19.7
5	85	10	12	.125	.270	216	678	37	5	71*	114*	161	997	53	5	.071	2.151	3030	16.1
6	118	107	91	.154	.183	119	766	586	77	95	121	127	1446	586	41	.066	.207	314	9.6
7	120	89	74	.222	.164	74	540	544	101	94	111	118	871	837	96	.108	.133	123	6.8
Mean Values	115	75	63	.176	.184	111	662	438	67	90	122	136	1129	668	59	.082	455	615	13.9
P Value†		<0.01			<0.50			<0.05			<0.001			<0.05			<0.30‡		

KEY TO ABBREVIATIONS:

GFRin = Glomerular filtration rate, ml./min. Inulin clearance

FF = Filtration fraction $\frac{\text{GFR}}{\text{RPF}}$

RPF = Total renal plasma flow, ml./min. — p-amino-hippurate clearance

MBP = Mean blood pressure, ⅓ pulse pressure plus diastolic pressure.

RVR = Renal vascular resistance $\frac{\text{MBP}}{\text{Renal Blood Flow}}$

C = Average of control values

M = Average of values during infusion of methoxamine

% = Change, expressed as per cent of control value (control = 100%)

* = Direct arterial mean blood pressure

† = See Table 1

‡ = Loses statistical significance because of one patient in whom the increase was very marked (5); if this value discarded then the increase for the remaining 6 patients is statistically significant. $P < 0.05$.

significantly reduced from control levels. Although there was no consistent change in the filtration fraction, crude total renal vascular resistance (RVR) was increased in all patients. The renal sodium excretion ($P<0.001$) (Table 3). Although these changes generally paralleled those in GFR there was no direct proportional relationship. Changes in potassium excretion were variable

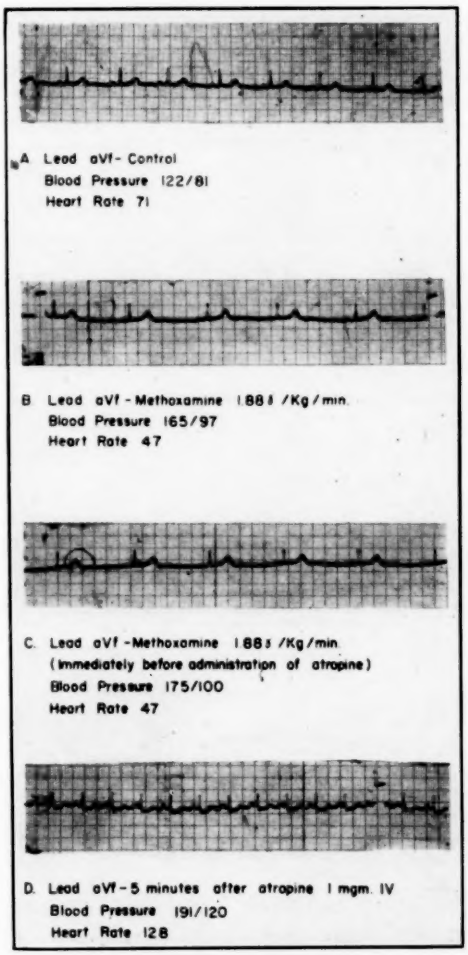
A Lead aVf - Control
Blood Pressure 122/81
Heart Rate 71
B Lead aVf - Methoxamine 1.88 s /Kg / min.
Blood Pressure 165/97
Heart Rate 47
C. Lead aVf - Methoxamine 1.88 s /Kg / min.
(immediately before administration of atropine)
Blood Pressure 175/100
Heart Rate 47
D. Lead aVf - 5 minutes after atropine 1 mgm. IV
Blood Pressure 191/120
Heart Rate 128

Fig. 2.—Effect of methoxamine on the electrocardiogram. In this patient there was significant S–T segment depression after administration of atropine.

hemodynamic response of one patient is shown in Fig. 3.

In addition to the changes in renal hemodynamics, there was a marked decrease in both urine flow ($P<0.01$) and and were unchanged in some patients in whom there was a marked decrease in both urine flow and sodium excretion.

Infusion of methoxamine was also

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associated with frequent side effects. The most common of these was a pilomotor response, which occurred in all of the patients. Spasm of the urinary bladder occurred in a few of the patients, and this was associated with the appearance of secretion from either the prostate or seminal vesicles. Central nervous system stimulation or other side effects were not encountered.

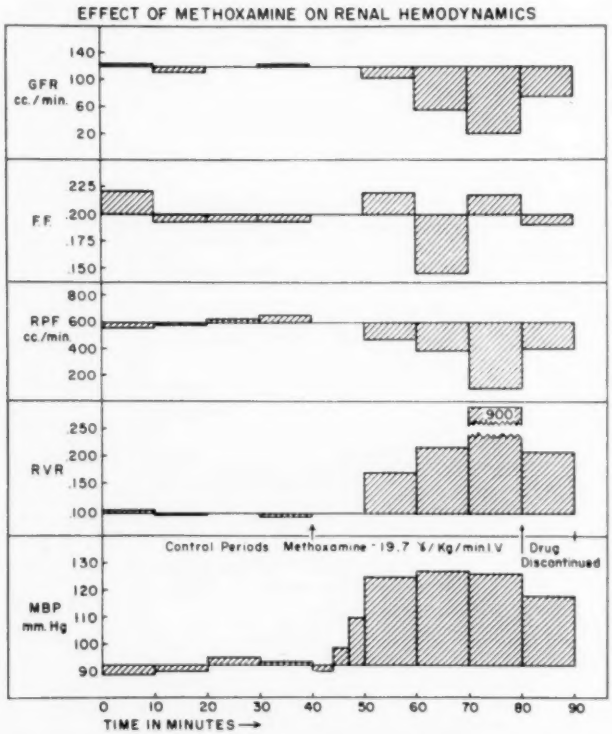

Fig. 3.—Typical renal hemodynamic changes observed during infusion of methoxamine.

Discussion. It is apparent from the data presented that methoxamine is a potent vasoconstrictor agent, and the side effects noted indicate that smooth muscle in other locations is affected as well. The depression of glomerular filtration rate (GFR) observed in many of the patients is in contrast to that previously observed during administration of norepinephrine (Mills, Moyer and Skelton[7]) epinephrine (Chasis *et al.*[1], and Ranges and Bradley[11]), ephedrine (Ranges and Bradley[11]), paredrinal (Ranges and Bradley[11]), Aramine (Livesay, Moyer and Chapman[5]), and phenylephrine (Crosley, Clark and Barker[2]) to human subjects, in whom there was either no change or only a slight depression of GFR. In Table 4 the renal effects of methoxamine, norepinephrine (Mills, Moyer and Skelton[7]), and Aramine (Livesay, Moyer and Chapman[5]) are compared. These studies were all done in the same clinic using exactly the same techniques. Although the blood pressure rise produced by the three drugs was not significantly different

TABLE 3.—EFFECT OF METHOXAMINE ON URINE FLOW AND EXCRETION OF ELECTROLYTES*

	UV			*GFR*in			*Na Excretion*			*K Excretion*		
Patient	*C*	*M*	*%*	*C*	*M*	*%*	*C*	*M*	*%*	*C*	*M*	*%*
1 . .	8.4	1.4	17	133	56	91	3.54	0.76	21	6.90	2.77	40
2 . .	12.4	0.9	7	103	85	83	6.35	1.39	22	3.51	3.48	99
3 . .	9.7	4.2	43	127	112	88	4.55	1.81	40	2.40	2.84	118
4 . .	1.2	0.3	25	119	64	54	5.33	0.97	18	1.59	1.40	88
5 . .	2.5	0.2	8	85	10	12	5.63	0.80	14	1.69	0.23	14
6 . .	13.5	5.3	39	118	107	91	5.81	4.17	72	2.78	2.41	87
7 . .	10.4	1.7	16	120	89	74	5.42	3.15	58	1.23	0.98	80
Mean Values	8.3	2.0	22	115	75	63	5.23	1.86	35	2.87	2.02	75
P value .		<0.01			<0.01			<0.001			<0.20	

* = For Key to Abbreviations See Tables 1 and 2.
UV = Urine Volume, ml./min.
Na Excretion = Excretion of sodium, mg./min.
K Excretion = Excretion of potassium, mg./min.

TABLE 4.—COMPARISON OF METHOXAMINE, NOREPINEPHRINE, AND ARAMINE ON RENAL HEMODYNAMICS*

	*GFR*in			*P Value*	*FF*			*P Value*	*RPF*			*P Value*	*MBP*			*P Value*	*RVR*			*P Value*	*Dose*
Drug	*C*	*D*	*%*	<	*C*	*D*	*%*	<	*C*	*D*	*%*	<	*C*	*D*	*%*	<	*C*	*D*	*%*		*mcg./kg./min.*
Methoxamine	115	75	63	0.01	.176	.184	111	0.50	662	438	67	0.05	90	122	136	0.001	.082	.455	615	0.30‡	13.90
Norepinephrine	120†	118	98	NS	.173	.284	167	0.001	706	417	60	0.001	97	132	136	0.001	.081	.195	224	0.001	0.32
Aramine	99	109	109	NS	.160	.180	120	0.001	653	589	92	0.10	86	125	147	0.001	.082	.128	162	0.001	1.70

* = For Key to Abbreviations See Table 2.
† = Creatinine clearance
D = Average values during administration of indicated drug
% = Per cent of control value. Control equals 100%.
‡ = More increase than with other drugs but due to extremely marked increase in 1 patient, the statistically significant change for the group was lost. When the observations for this patient are omitted then the increase for the remaining 6 patients is statistically significant ($p<0,05$). See Table 2.

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(analyzed by statistical comparison of the means), there was no significant decrease in GFR or renal plasma flow (RPF) during infusion of Aramine, whereas with norepinephrine, RPF was significantly depressed ($P<0.001$) and with methoxamine both GFR ($P<0.01$) and RPF ($P<0.05$) were depressed. These observations suggest the possibility that adrenergic receptors in certain vascular beds of the body may vary in their sensitivity to sympathicomimetic drugs of different chemical configurations, and suggest that methoxamine may have a more selective effect on renal vascular adrenergic receptors than norepinephrine or Aramine. However, this interpretation may have to be modified, when further information is available concerning the effect of methoxamine on cardiac output, since if a given drug led to a fall in cardiac output, significantly more vasoconstriction might be required by such a drug to produce an identical rise in blood pressure as compared to drugs such as epinephrine (Goldenberg *et al.*[3]) which causes a rise in cardiac output or Aramine which produces no change in cardiac output (Livesay, Moyer and Chapman[5]). Administration of norepinephrine is usually associated with a slight fall in cardiac output (Goldenberg *et al.*[3]), but no data has been reported concerning the effects of methoxamine in this regard. Therefore, the results observed here may be on this basis rather than due to selective renal vasoconstriction; however, preliminary studies (Mills, Moyer and Handley[6]) on renal function following direct injection of various sympathicomimetic drugs into the renal artery of dogs, indicate that the renal vessels are much more sensitive to methoxamine than to the other agents tested.

Administration of norepinephrine and epinephrine to dogs (Moyer and Handley[8]) has produced changes in GFR and RPF similar to those in the present study. The changes in dogs were demonstrated to be a result of a decrease in the number of active nephron units, by simultaneous measurement of the maximal tubular transport of glucose (TmG). Infusion of methoxamine in dogs (Mills, Moyer and Handley[6]) also produces similar changes in GFR and RPF but these are again more marked than with norepinephrine or epinephrine, and it seems that the dog renal vascular adrenergic receptors are considerably more sensitive to sympathicomimetic agents than is the case in humans. As no data is presently available in humans as to the effects of methoxamine on maximal tubular function, one can only speculate as to the true nature of the depression of GFR and RPF in these patients; however, there seems to be two likely possibilities. The first and probably most likely in view of other studies (Chasis *et al.*[1], Crosley, Clark and Barker[2], Livesay, Moyer and Chapman[5], Mills, Moyer and Skelton[7], and Ranges and Bradley[11]) is that the observed changes were a result of intense renal vascular constriction affecting all of the renal arterioles resulting in decreased blood flow through each individual nephron unit. An alternate possibility in view of the animal studies (Moyer and Handley[8]) is that there was a reduction in the number of active nephron units, also due to renal vasoconstriction, but neither theory can be proved until further data are obtained by measurement of maximal tubular transport of glucose or p-amino-hippuric acid.

Although it cannot be definitely stated from this study that the renal hemodynamic response to methoxamine would be similar during the treatment of an acute hypotensive episode, the fact that there was a depression of glomerular filtration rate in the

normal patient, suggests that if it is used for treatment of shock over a prolonged period, that renal function should be carefully appraised.

Conclusions. 1. Administration of methoxamine to seven normal human subjects resulted in a significant depression of glomerular filtration rate and renal plasma flow, associated with a marked increase in renal vascular resistance. Urine volume and sodium excretion were also depressed. Comparison of the renal effects of methoxamine to those produced by norepinephrine and Aramine indicates that there is considerably more renal vasoconstriction for a given blood pressure rise when methoxamine is given.

2. It is postulated that adrenergic receptors in individual vascular beds may vary in sensitivity to a given sympathicomimetic drug.

3. In the treatment of patients with hypotensive emergencies, particularly when there is evidence of depression of renal function, pressor amines which have less renal effects than methoxamine such as Aramine, phenylephrine or norepinephrine would be a more logical choice for initial therapy.

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SUMMARIO IN INTERLINGUA

Methoxamina: Effecto Super le Pression Sanguinee e le Hemodynamica Renal

1. Le administration de methoxamina a septe normal subjectos human resultava in un relentation significative del filtration glomerular e del fluxo renal de plasma, associate con marcate grados de augmento in le resistentia renovascular. Le volumine del urina e le excretion de natrium esseva etiam deprimite. Le comparation del effectos renal de methoxamina con le effectos renal producite per norepinephrina e Aramina indica que le vasoconstriction renal correspondente a un specific augmento del pression sanguinee es considerabilemente plus forte quando le droga usate es methoxamina.

2. Es postulate que le receptores adrenergic in varie vasculaturas individual pote variar in lor sensibilitate pro un specific droga sympathicomimetic.

3. In le tractamento de urgentia de patientes con hypotension, specialmente in le presentia de indicios de deprimite functiones renal, aminas pressori con minus pronunciate effectos renal que methoxamina, *i.e.* per exemplo Aramina, phenylephrina, o norepinephrina, esserea un selection plus logic pro le therapia initial.

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EFFECT OF CENTRALLY ACTIVE DRUGS ON CONDITIONING IN MAN:* THE INHIBITING AND FACILITATING EFFECTS OF CHLORPROMAZINE, AMOBARBITAL AND METHYLPHENIDYLACETATE ON THE CONDITIONED GALVANIC SKIN RESPONSE

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The recent heightened interest in new agents which affect the higher neural centers has increased the desirability of studying some of the subtle effects of these agents on human behavior using objective measurements. Since Pavlov, the conditioning of reflexes has been recognized as a valuable method for studying the function of the nervous system in behavior. This technique has been employed extensively in infrahuman animals (Evans[2], Fellows[3], Gantt[7], Jacobsen and Skaarup[11], Jacobsen and Sonne[12], Lewin[14], Wentink[18], and Wolff and Gantt[21]) and to a more limited extent in human beings (Finkelstein, Alpern and Gantt[5], Switzer[16], and Winsor[20]) in studying the influences of various types of centrally acting drugs on the acquisition and extinction of conditioned reactions. In general, in man and in lower animals, depressant drugs[2,7,11,12,14,18,21] were found to suppress conditioned responses already established, whereas stimulants[2,5,16,21] facilitated acquisition and reduced the rate of extinction of such responses.

In this investigation we have studied the effects of two depressants, amobarbital (Amytal) and chlorpromazine (Thorazine) and a stimulant, methylphenidylacetate (Ritalin, an amphetamine-like compound), on two aspects of conditioning. The study was designed to determine what effect these agents would have on (1) spontaneous recovery and (2) reconditioning of the galvanic skin response (GSR) in human subjects in whom the reflex had been previously conditioned and then extinguished.

We chose to study the GSR because it is easily recorded, readily conditioned in human subjects and represents an autonomic response involved in emotional reactions (Woodworth and Schlosberg[22]). The response was conditioned and extinguished one day and 24 hours later the effects of the drugs, which were administered two hours prior, were determined on the sponta-

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neous recovery from the previous day's extinction and on the reconditioning of the same response.

Methods. SUBJECTS. Forty individuals, 24 females and 16 males ranging in age from 14 to 77 (mean age of 39) were conditioned twice on consecutive days. Thirty-four were convalescent patients from a medical service who were suffering from a variety of disorders, but who at time of testing were recovered and were semi-ambulatory and were not receiving centrally active drugs. Six subjects were healthy volunteers. Twelve of these 40 subjects acted as controls and received no drug. The remaining 28 subjects were divided into 3 drug groups. On the second day, 9 received 200 mg. Sodium Amytal I.M., 8 received 50 mg. Thorazine orally and 11 received 30 mg. Ritalin orally. The drugs were administered 2 hours before the procedure.

PROCEDURE. The GSR was recorded from the left palm on the Keeler Polygraph, Model 302*. The unconditioned stimulus (US) was a small AC current delivered to the right palm and right index finger which were resting on two copper plates, 50 and 3 square cm. in area respectively. The magnitude of the current varied from 0.1 to 6.0 ma, depending on individual subjective tolerance, and it was kept constant for each subject on both days. The conditioned stimulus (CS) was a one-second exposure from a 7-watt lamp mounted 18 inches from the subject just below eye level. The subject was comfortably seated with both arms and hands resting on a table and was separated and completely screened from the experimenter. The intervals between the CS and US and the time of appearance of each separately were controlled by an electronic stimulus timer and these events were recorded simultaneously with the GSR on the polygraph. A partial reinforcement, short-trace procedure was used in which the CS lasted 1 second and approximately 0.5 second later the US was presented for 2 seconds.

FIRST DAY: There were four main steps to the first day's procedure. First, the GSR to the CS was adapted out. The criterion for adaptation was three consecutive GSR's whose magnitudes were each less than 1/16 inch on the recording (1 inch equals 2000 ohms), or until 30 presentations of the CS had been given. Second, the GSR response to the US was recorded 5 times successively at 20-second intervals. Third, a partial reinforcement type of training was undertaken consisting of twenty trials at intervals varying in a random fashion from 20 to 40 seconds. Fifteen of the trials were reinforced (CS followed by US) and 5 were the CS alone at random. Fourth, following training, the CS was presented at 20-second intervals until the subject's GSR was extinguished (*1st extinction*), utilizing the criterion described for adaptation. The number of lights presented to meet the criterion for extinction was used as the measure of strength of conditioning.

SECOND DAY: The subjects returned at approximately the same time the following day and the same four steps of the previous day's procedure were repeated. The CS was presented alone until the criterion was met (*2nd extinction*), and the number of such trials was used in determining the extent of the subject's "spontaneous recovery" of the condition reflex. The recording of the five reactions to the US alone, the conditioning and the extinction (*3rd extinction*) were carried out as before. The number of lights required to meet the criterion during the 3rd extinction was used in determining the extent of "reconditioning."

Each individual was used as his own control in determining the effects of the drugs upon spontaneous recovery and reconditioning. The drug effects were determined for: (1) *spontaneous recovery* by obtaining intra-individual differences between 1st extinction and 2nd extinction; (2) *reconditioning* by obtaining intra-individual differences between 1st extinction and 3rd extinction. In both cases these intra-individual differences were derived by subtracting the number of trials to the criterion for 1st extinction from the number of trials to the criterion for 2nd extinction or 3rd extinction. The means of these difference-scores for each of the three drug groups were compared with the means of the difference-scores for the control group.

Results. REACTION TO SHOCK ALONE (US) IN THE FOUR GROUPS ON THE FIRST AND SECOND DAYS. The total magnitude of the GSR (ohms) to the five shocks alone were determined for each subject on both the first and second days. Intra-individual differences were obtained by subtracting second day values from those of the first day and the means of these differences are shown in Table 1. None of the means for the drug groups were significantly differ-

*Associated Research Inc., 3758 West Belmont Avenue, Chicago 18.

ent* from the control mean so that drug effects on the conditioned response could not be attributed to inhibition or facilitation of a subject's response to shock alone.

TABLE 1.—MEANS OF THE DIFFERENCES BETWEEN GSR AMPLITUDE (IN OHMS) TO US (SHOCK) ALONE ON THE 1st DAY AND ON THE 2nd DAY. NONE OF THE MEANS FOR THE DRUG GROUPS WAS SIGNIFICANTLY DIFFERENT FROM THE CONTROL INDICATING THAT THE DRUGS HAD NO SIGNIFICANT EFFECT ON THE UNCONDITIONED RESPONSE.

	GSR (10^3 Ohms) to Shock Alone (1st Day's Values Minus 2nd Day's)			
	Control	*Amytal*	*Thorazine*	*Ritalin*
Mean	0.51	−0.22	−2.82	−0.80

TABLE 2.—MEAN NUMBER OF TRIALS TO EXTINCTION FOR THE 1st EXTINCTION PERIOD (NO-DRUG DAY) IN THE CONTROL AND EACH OF THE DRUG GROUPS. STATISTICAL ANALYSIS SHOWED NO SIGNIFICANT DIFFERENCES IMPLYING THAT THE FOUR GROUPS ON THIS FIRST DAY WERE EQUALLY CONDITIONABLE.

	Mean No. CS's Presented to Meet Criterion of Extinction			
	Control (N=12)	*Amytal (N=9)*	*Thorazine (N=8)*	*Ritalin (N=11)*
1st Extinction (No-drug day)	10.4	18.2	15.9	8.5

EXTENT OF CONDITIONING (1ST EXTINCTION) IN ALL GROUPS ON THE FIRST DAY. The mean number of trials to extinction (a measure of extent of conditioning) for the control and drug groups on the first day varied from 8.5 to 18.2. When the drug group means were compared statistically to the control mean (Table 2) no significant differences were found. Thus, it can be said that the four groups were from comparable populations in terms of degree of conditioning on the first day.

TABLE 3.—MEANS FOR SPONTANEOUS RECOVERY AND RECONDITIONING IN THE CONTROL AND EACH OF THE THREE DRUG GROUPS. THE MEANS ARE BASED ON INTRA-INDIVIDUAL DIFFERENCE-SCORES WHICH WERE DERIVED BY SUBTRACTING THE NUMBER OF CS's PRESENTED DURING THE 2nd EXTINCTION AND 3rd EXTINCTION PERIODS FROM THE NUMBER OF CS's PRESENTED DURING THE 1st EXTINCTION PERIOD FOR SPONTANEOUS RECOVERY AND RECONDITIONING RESPECTIVELY.

	Mean No. CS's Presented to Meet Criterion of Extinction			
	Control (N=12)	*Amytal (N=9)*	*Thorazine (N=8)*	*Ritalin (N=11)*
Spontaneous Recovery	3.6	−9.0*	− 2.5	4.8
Reconditioning	−1.9	−8.4	−10.4*	6.5†

*P<.01 †P<.05

P values indicate a significant difference between the control group mean and the respective drug group mean.

CONTROL GROUP. The control group had a mean for the 2nd extinction (2nd day) of 14.0 trials compared to a mean of 10.4 trials for 1st extinction. The difference between these two means was 3.6 trials (2nd extinction minus 1st extinction) which was significant† (P<.02) and indicated that "spontaneous recovery" exceeded first day's conditioning. This is shown in Table 3 and graphically in Fig. 1 where these

*Nonparametric statistics were used in analyzing all the results since the data were not normally distributed and the variances were not homogeneous as determined by the Bartlett Test (Johnson[13]). The Festinger[4] Test was used to determine the significance of the difference between means which were based on unequal N's.

†Wilcoxon's[19] nonparametric test for paired deviates was used in analyzing the results in the control group.

values are also shown for the drug groups. The 3rd extinction period showed a mean of 8.5 trials. Thus the mean for reconditioning, which is determined by subtracting the mean for 1st extinction from that of the 3rd extinction, is −1.9 (see Table 3 and Fig. 1—"Extent of Reconditioning"). This difference is not statistically significant. These results for the control group are compared with the results in the drug groups in Fig. 1 and Table 3 in determining the drug effects given below.

AMYTAL GROUP. Spontaneous recovery in this group was substantially reduced, the mean being −9.0 compared to the control mean of 3.6. The difference between these two means is significant ($P<.01$). The extent of reconditioning was also reduced but not significantly so when the mean of −8.4 was compared to the control mean of −1.9 ($P>.05$).

THORAZINE GROUP. Spontaneous recovery mean was −2.5 compared to 3.9 for the controls which was only suggestive of a decrease ($P>.05$). However, reconditioning was significantly reduced (−10.4 compared to −1.9 for the controls; $P<.01$).

RITALIN GROUP. Spontaneous recovery was essentially the same (mean of 4.8 compared to 3.6 for controls) as in the no-drug subjects. But reconditioning was strikingly increased (mean 6.5) compared to controls (mean −1.9) and this difference was significant at the 5% level of confidence.

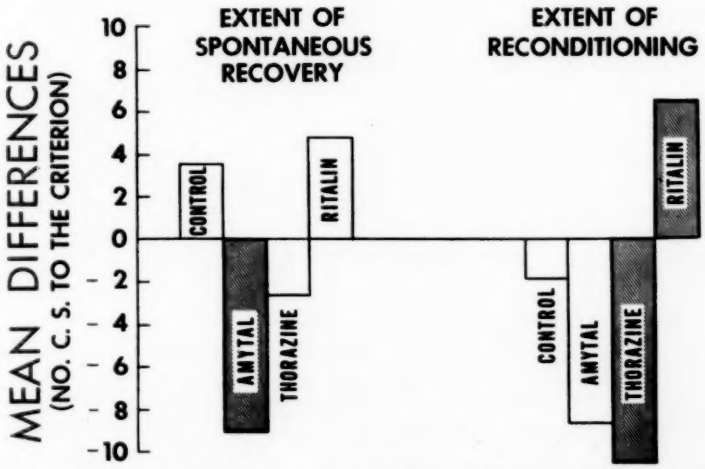

Fig. 1.—The effects of Amytal, Thorazine and Ritalin upon spontaneous recovery and reconditioning compared to the no-drug control. The mean differences were derived from intra-individual difference-scores which were obtained by subtracting the number of CS's required to reach the criterion of extinction for spontaneous recovery and reconditioning. Positive values indicate a gain and negative values a loss in extent of conditioning. The cross-hatched bars indicate statistically significant values.

Discussion. Our results appear to be in general agreement with others who have studied the effects of centrally active agents on various aspects of conditioning. However, it should be pointed out that in this study we specifically investigated the effects of CNS agents on the retention and relearning of an emotional response. In this respect our study is unique and, therefore, not entirely comparable to other related studies.

It is reasonable to assume that the

drugs acted on the conditioned reflex and not on the unconditioned response since the reaction to shock alone was no more different from day to day in the subjects receiving the drugs than in the control group.

The results in the no-drug control subjects indicated the degree of habituation to our experimental procedure. Surprisingly the extent of spontaneous recovery in this group was greater than the original conditioning. We have no explanation for this except that possibly the subjects were more apprehensive on the second day, since it has been shown that subjects who rate high on manifest anxiety scales condition more easily (Spence and Farber[15], and Taylor and Spence[17]). Reconditioning in the controls was slightly less than first day's conditioning which suggests a degree of habituation.

Our findings confirm those of others who found that drugs are capable of modifying a conditioned response. What processes are involved in conditioning cannot as yet be expressed in strictly neurophysiological terms. However, Gellhorn[8,9,10] interprets these drug actions as being due to their alteration of the excitability of cortical and subcortical structures, that is, stimulants raise (facilitate) and depressants partially abolish (inhibit) this reactivity. Brady[1] emphasizes the subcortical structures, those of the limbic system, as the possible site of variability in conditioned responses. He has shown that lesions in the habenular complex of the thalamus, septal region, hippocampus and the amygdaloid nuclei of rats interfere with the conditioned response and that electrical stimulation of the caudate nucleus of rats, cats and monkeys prevents inhibition (facilitation) of conditioned responses. Viewed psychologically, our results could possibly be explained by the ability of these agents to alter tension and anxiety in our subjects. Freeman[6] has shown experimentally that tension both inhibits and facilitates learning, that there is seemingly an optimum degree of tension for learning. Spence and Farber[15] and Taylor and Spence[17] found that subjects who tested high on manifest anxiety scales, conditioned more easily than those with low scores.

Summary. A study of the effects of two depressant type drugs (Amytal and Thorazine) and a stimulant (Ritalin) on the conditioned GSR is presented. The GSR was conditioned and extinguished in 41 subjects; 24 hours later these subjects were divided into a control and three drug groups and one of the experimental drugs was given to the subjects in each of the drug groups 2 hours before spontaneous recovery and reconditioning was tested. The results were as follows:

(1) Reaction to the unconditioned stimulus (shock) was not affected by any of the drugs.
(2) Amytal inhibited spontaneous recovery; there was a tendency for it to inhibit reconditioning but this effect was not significant.
(3) Thorazine had a significant inhibitory effect upon reconditioning, but did not substantially alter spontaneous recovery.
(4) Ritalin facilitated reconditioning but did not significantly alter spontaneous recovery.

The physiological and psychological implications of these results are discussed.

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SUMMARIO IN INTERLINGUA

Le Effecto de Drogas a Action Central Super le Conditionamento in Humanos: Le Effectos Inhibitori e Facilitatori Exercite per Chlorpromazina, Amobarbital, e Methylphenidylacetato Super le Conditionate Responsa Cutanee Galvanic

Es presentate un studio del effectos exercite per duo drogas del typo depressori, Amytal (amobarbital) e Thorazina (chlorpromazina), e un droga stimulante, Ritalina (methylphenidylacetato), super le conditionate responsa cutanee galvanic. Iste responsa esseva conditionate e extinguite in 41 subjectos. Vinti-quatro horas plus tarde iste subjectos esseva dividite in quatro gruppos (un de controlo e tres a droga), e un del agentes del experimento esseva administrate a omne le subjectos in cata un del gruppos a droga 2 horas ante que le recuperation spontanee e le reconditionamento esseva testate. Le resultatos esseva le sequente.

(1) Le reaction al stimulo non-conditionate (choc) non esseva afficite per ulle del drogas.

(2) Amytal inhibiva le recuperation spontanee. Illo tendeva a inhibir le reconditionamento, sed iste effecto non esseva significative.

(3) Thorazina exerceva un significative effecto inhibitori super le reconditionamento, sed illo non alterava le recuperation spontanee a grados notabile.

(4) Ritalina facilitava le reconditionamento sed non alterava de maniera significative le recuperation spontanee.

Le importantia de iste resultatos ab le puncto de vista physiologic e psychologic es discutite.

THE EFFECT OF CHLORISONDAMINE ON RENAL HEMODYNAMICS IN HYPERTENSIVE PATIENTS*

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Ganglionic blocking agents, such as hexamethonium (Mills and Moyer[5]) and pentolinium (Moyer and Hershberger[6], and Rønnov-Jessen[7]), when injected intravenously, usually cause a decrease in glomerular filtration rate and renal plasma flow. This reduction of renal function has been considered to be one of the disadvantages of this class of compounds in the treatment of hypertension. Chlorisondamine (Ecolid†), an unsymmetric quarternary ganglionic blocking agent, was administered intravenously to hypertensive patients in the present study to determine its effect on renal hemodynamics.

Methods and Materials. Ten severe hypertensive patients were selected for the study. There were 6 females and 4 males. The age range was 28 to 55 years, with a mean of 40.8 years. The mean blood pressure range after bed rest was 138 to 177 mm. of mercury, with a mean of 157 mm. mercury. Funduscopic examinatioin revealed grades II to IV hypertensive retinopathy. All the patients had left ventricular hypertrophy by physical examination and by roentgenogram, and 5 patients had had previous episodes of congestive heart failure. Five patients also had had previous cerebrovascular thrombosis.

The patients were observed at bed rest for 3 to 19 days (mean 10.8 days) before renal function tests were conducted. Only one patient (R.W.) was observed less than 6 days; she had been followed in the outpatient department prior to hospitalization. All previous ganglionic blocking agents were discontinued upon admission to the hospital. All subjects were in cardiac compensation at the time of testing, as determined clinically, and as measured by venous pressure and circulation time in seven of the ten patients.

Renal function studies were performed in the morning with the patient in the fasting state. The subjects were instructed to drink one liter of water during the hour prior to the test and were given additional water during the observation. Throughout the entire study, the patients were lying in a bed tilted to a 30 degree angle from the horizontal with the head up.

The glomerular filtration rate and effective renal plasma flow were measured by the determination of the clearance of inulin and para-amino-hippurate, respectively, according to the method of Goldring and Chasis[3]. Inulin was determined by Schreiner's modification of Roe's method[8]. Para-aminohippurate was determined by Smith's method[10]. The mean of three 10-minute periods was used for each value recorded in Table 1. All values were corrected to 1.73 square meters body surface area.

Ecolid was administered intravenously in doses ranging from 2.5 to 10 mg. over a period of one to 30 minutes, depending on

*This work was supported by the Michigan Heart Association and research grant H–1471 from the National Heart Institute of the National Institutes of Health, Public Health Service.

†The Ecolid used in this study was generously supplied by Dr. C. H. Sullivan of the Ciba Pharmaceutical Products, Inc., Summit, N.J.

TABLE 1.—CHANGES IN BLOOD PRESSURE AND RENAL HEMODYNAMICS FOLLOWING INTRAVENOUS CHLORISONDAMINE

Patient	Age	Sex	Ecolid I. V. mg.	Mean Blood Pressure mm./Hg			Glomerular Filtration Rate* ml./min.			Renal Plasma Flow* ml./min.			Total Renal Resistance (dynes-sec./cm.^{5})10^3		
				Control	1 hr.	2 hr.	Control	1 hr.	2 hr.	Control	1 hr.	2 hr.	Control	1 hr.	2 hr.
J.R.	43	M	10	159	109	110	29	19	18	119	90	90	55.0	48.3	48.8
G.D.	29	F	7	175	116	118	42	32	24	140	148	100	55.1	33.5	50.1
H.H.	36	M	5	160	107	108	68	48	57	175	183	181	39.6	24.4	24.9
L.M.	55	M	2.5	149	121	142	78	53	58	286	229	257	20.3	20.2	21.4
E.L.	40	F	6	177	115	105	60	36	32	225	171	178	37.4	30.9	26.9
R.W.	36	F	5	145	95	108	86	61	85	356	352	390	16.3	10.4	10.8
L.B.	51	F	5	138	87	91	73	62	76	295	377	389	19.1	10.1	9.2
R.M.	28	M	3	145	83	90	75	27	52	320	144	306	20.9	25.2	13.0
R.P.	48	F	2.5	151	108	116	77	60	67	352	382	370	18.2	11.6	13.1
M.D.	42	F	9	172	96	102	76	52	67	393	426	395	18.1	9.0	10.3

* Corrected to 1.73 m^2 body surface area.

TABLE 2.—PERCENTILE CHANGES FOLLOWING INTRAVENOUS CHLORISONDAMINE

Patient	% Change from Control Mean BP		% Change from Control GFR		% Change from Control RPF		% Change from Control Resistance	
	1 hr.	2 hr.	1 hr.	2 hr.	1 hr.	2 hr.	1 hr.	2 hr.
J.R.	−31	−31	−34	−38	−24	−24	−12	−11
G.D.	−34	−32	−24	−43	+ 6	−29	−39	− 9
H.H.	−33	−32	−29	−16	+ 5	+ 3	−38	−37
L.M.	−19	− 5	−32	−26	−20	−10	0	+ 5
E.L.	−35	−41	−40	−47	−24	−21	−17	−28
R.W.	−34	−26	−29	− 1	− 1	+10	−36	−33
L.B.	−37	−34	−15	+ 4	+28	+32	−47	−52
R.M.	−43	−38	−64	−31	−55	− 4	+21	−39
R.P.	−28	−23	−22	−13	+ 9	+ 5	−36	−28
M.D.	−44	−41	−32	−12	+19	+ 1	−50	−43
Mean	−34	−30	−32	−22	− 6	− 4	−25	−28

the blood pressure fall. The clearances of inulin and para-aminohippurate were measured one and 2 hours afer the start of Ecolid administration. Blood pressure was recorded by sphygmomanometer at least every 5 minutes. The diastolic pressure was taken to be that reading at the point of disappearance of all sound. Mean blood pressure was calculated as one-third the pulse pressure plus the diastolic pressure. Total resistance was calculated from the formula of Gomez, as quoted by Smith[9]:

$$R = \frac{Pm - Pv}{RBF} \times 1328 \times 60,$$

where

R is total renal resistance in dynes-seconds/cm^5

Pm is mean arterial pressure (mm. Hg)

Pv is mean renal venous pressure, assumed to be equal to 10 mm. mercury

RBF is renal blood flow (ml./minute), calculated from the effective renal plasma flow:

$$RBF = \frac{RPF}{(1 - \text{hematocrit})}$$

Results. The results are summarized in Table 1. In Table 2, the figures are expressed in terms of percentage change from the control values. The mean blood pressure was lower than the control at both the first and second hours after Ecolid in all patients, the fall ranging from 7 to 76 mm. of mercury. For the whole group, and expressed as percentage change, the decrease in mean blood pressure was 34% at the end of the first hour, and 30% at the end of the second hour.

The mean glomerular filtration rate, compared to the control, was decreased by 32% at one hour; by the second hour, it had risen back towards the control figure, so that the decrease from control was only 22%. This rise was significant, the probability of its having occurred by chance alone being less than 5%.

The mean percentage change in renal plasma flow for the group was only —6% at the first hour, and —4% at the second hour. The impression that these changes are not significantly different from zero is borne out by the standard errors of these two means, which are ±8% and ±6% respectively. Although the *mean* change in renal plasma flow was not significant, there was much variation, in both directions, in each individual. At the end of one hour, 5 patients had a decrease, 4 patients had no significant change, and one patient had an increase in renal plasma flow, if any change greater than 10% of the control value is considered to be significant. Likewise, at the second hour, 4 patients had a decrease, 4 patients had no significant change, and 2 patients had an increase in renal plasma flow.

At both the first and second hours, 8 of the 10 subjects showed a decrease of more than 10% in total renal resistance, giving a mean decrease for the group of 25% and 28% respectively.

Discussion. Decrease in cardiac output, probably due to pooling of blood in the dependent portions, resulting in diminished venous return, is an important factor in the hypotension produced by ganglionic blocking agents (Freis *et al.*[1], and Hoobler *et al.*[4]). It is responsible for the postural hypotensive effect noted with this class of drugs. On the other hand, decreased peripheral resistance has also been noted as a factor in the reduction of blood pressure with their use (Gilmore *et al.*[2], Mills and Moyer[5], Moyer and Hershberger[6], and Werkö *et al.*[11]). In order not to minimize the first factor, the study was conducted in the head up tilt position. The amount of elevation chosen, 30 degrees, represents a compromise between a desirability for the erect position and the comfort of the patients.

The fall in glomerular filtration rate was consistent in all patients studied and agrees with the findings of others working with hexamethonium and

pentolinium (Mills and Moyer[5], Moyer and Hershberger[6], and Rønnov-Jessen[7]); however, whereas previous studies have usually shown a decrease in renal plasma flow following the administration of a ganglionic blocking agent, the present investigation showed a marked variability in the direction and magnitude of response of the renal plasma flow to the injection of Ecolid in doses causing a significant decrease in blood pressure. What was responsible for this individual variation? Renal plasma flow is inversely proportional to total renal vascular resistance, and directly proportional to the pressure drop between renal artery and renal vein. Since renal vein pressure, which was assumed to be 10 mm. of mercury, is quite small compared to mean arterial pressure, it may be disregarded, giving the following relationship:

$$\text{renal plasma flow} \propto \frac{\text{mean arterial blood pressure}}{\text{renal vascular resisitance}}$$

The data were then examined to ascertain, if possible, which of the two variables, mean blood pressure or renal resistance, was responsible for determining how the renal plasma flow changed in response to Ecolid. A scattergram, relating, for each experiment, change in renal plasma flow to change in mean arterial blood pressure was constructed (Fig. 1). It can be seen that there is no apparent relationship between these two factors. The calculated coefficient of correlation was 0.019. This would indicate that the magnitude of decrease in mean blood pressure was not the factor determining how the renal plasma flow changed. In the second scatter diagram (Fig. 2), the change in renal plasma flow was plotted against the change in total renal resistance. Inspection reveals a relationship, such that in experiments where renal resistance did not change, or rose, the renal plasma flow fell markedly, and where renal resistance did fall significantly, the renal plasma flow did not change much or actually increased. The coefficient of correlation here was -0.89, a highly significant figure ($p<0.001$). Under the present experimental conditions, then, whether the renal plasma flow will decrease, not change, or increase in response to hypotensive doses of Ecolid seems to depend chiefly on the degree to which renal resistance is capable of decreasing.

The lack of fall in renal plasma flow following Ecolid, which occurred thirteen times out of twenty measurements in these 10 subjects, is an unusual finding in that previous work with hexamethonium and pentolinium have shown usually a decrease in renal plasma flow. It has been demonstrated that cardiac output, following the administraion of a ganglionic blocking agent, may *increase* in patients who are in heart failure (Freis *et al.*[1]). This could account for a rise in renal plasma flow; however, of the 6 patients in the present study who showed either a rise or no significant change in renal plasma flow, 5 had normal venous pressure and circulation time. All 6 were considered to be in cardiac compensation on the basis of clinical examination. Cardiac output was not measured in these subjects.

It was not possible to predict how Ecolid would change the renal plasma flow on the basis of age, degree of vascular damage in the optic fundi, duration of the disease, severity of the hypertension, or degree of renal impairment.

Summary. The ganglionic blocking agent, Ecolid, was administered intravenously to 10 hypertensive subjects lying on a bed tilted 30 degrees from the horizontal. Glomeruler filtration

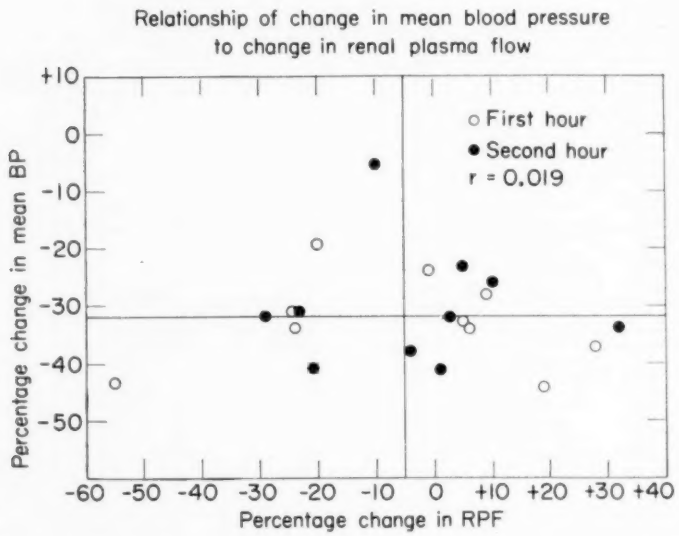

Fig. 1.—Relationship of change in mean blood pressure to change in renal plasma flow.

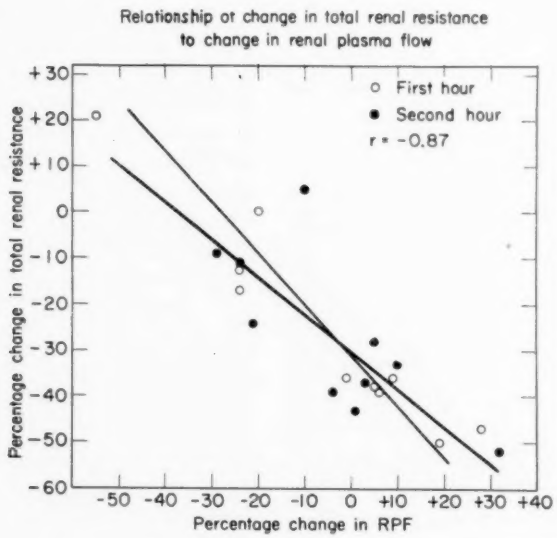

Fig. 2.—Relationship of change in total renal resistance to change in renal plasma flow.

rate and renal plasma flow were measured before and one and 2 hours after the injection. The mean blood pressure fell about one-third of the control value; the glomerular filtration rate fell 32% at one hour, and tended to return toward the control value at the second hour. Total renal resistance fell by about one-quarter of the control figure. There was a wide variation in the response of the renal plasma flow to Ecolid. How the renal plasma flow changed seemed not to depend so much on the magnitude of fall of the mean blood pressure as on the extent of fall in total renal resistance.

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SUMMARIO IN INTERLINGUA

Le Effecto de Chlorisondamina Super le Hemodynamica Renal in Patientes Hypertensive

Le agente de blocage ganglionic, Ecolido, esseva administrate intravenosemente a 10 subjectos hypertensive reposante super un lecto basculate a un angulo de 30 grados ab le plano horizontal. Le filtration glomerular e le fluxo de plasma renal esseva determinate ante le injection e 1 e 2 horas post illo. Le pression sanguinee medie se reduceva per circa un tertio del valor de controlo. Le filtration glomerular esseva relentate per 32% un hora post le injection e monstrava un tendentia de retornar verso le valor de controlo al fin del secunde hora. Le resistentia renal total se reduceva per circa un quarto del valor de controlo. Esseva notate extense variationes in le responsas del fluxo de plasma renal post injectiones de Ecolido. Le forma specific del alterationes in le fluxo de plasma renal pareva depender non tanto del magnitude del reduction del pression sanguinee medie como plus tosto del magnitude del reduction del total resistentia renal.

THE USE AND ABUSE OF STEROID THERAPY, NOTABLY IN ALLERGIC DISORDERS*

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Those, who in 1949 at the meeting of the Association of American Physicians heard Hench and Kendall[2] describe the effects of cortisone and ACTH in patients with rheumatoid arthritis and acute rheumatic fever, and saw the motion pictures portraying those effects, will never forget that dramatic moment. The great promise which that "Preliminary Report" implied has been abundantly fulfilled in the intervening years. These have witnessed the development of a group of substances which have brought relief and hope to countless sufferers from a wide range of serious and crippling diseases, while in the hands of scientists they have proved invaluable tools for research.

The more powerful a remedy, the greater is its potential for harmful as well as helpful effects. These effects, both good and bad, will eventually define the limitations of the remedy, and the indications and contraindications for its use. A rapidly growing experience in the hands of many careful observers has now made it possible to formulate a number of rules that underlie a safe and rational use of steroid therapy. Unfortunately, there are also accumulating far too many examples of the unwise use of these substances. Indeed, the abuse of steroid therapy is widespread and its consequences are serious. Of all the diseases amenable to steroid therapy, those due to allergy not only are the most frequent, but they also provide a disproportionately large number of instances of such therapeutic abuse. Therefore, it is timely to call attention to the accumulated experience, especially as it reveals the dangers of steroid therapy, and to restate the principles that underlie its proper use.

Let me first indulge in a bit of teleological speculation.

Of all man's adversaries, the rat has proved the most capable. (For completeness one might add the staphylococcus.) The rat has chosen to live off the human economy, and if the yearly damage to man's foods and possessions could be accurately assessed, it would prove to be a tremendous levy. The rat has followed man wherever he has gone and has traveled not only in his footsteps but by every new means of conveyance: trains, ships, and planes. The rat has been, and continues to be, the reservoir and vector of a number of man's diseases, be it the plague that marched with the black rat across Europe from the 13th to the 16th centuries and from the crossing of the Bosporus to the crossing of the English Channel, and that probably the Norway rat brought to our west coast at the turn of this century, and so to other wild rodents that now harbor the plague bacillus in at

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least a dozen western states; or be it the leptospiroses in many places, including Philadelphia and on this very day. Those who have not read the book, are urged to read Hans Zinsser's classic of medical and philosophical writing: *Rats, Lice and History*[3].

Man is at a disadvantage in his struggle to control the rat. The rat hides himself very efficiently. It has been shown that if 3 or 4 rats are seen about the premises, the census of their colony is 300 or 400. The rat is hard to exterminate by poisons, in spite of its inability to vomit, for the colony is warned by a few foolish tasters, so that the rest shun the bait.

For many reasons, then, the rat has been studied more intensively than has any other creature. Indeed, in several respects more is known about the rat than about man himself. The Wistar rat, propagated in the Wistar Institute here in Philadelphia now for over 250 generations, is the best standardized animal in the world: under given circumstances of diet and environment, one can predict all sorts of data on size, structure and function. The Wistar strain is, therefore, extensively used in laboratories all over the world, since the information available about it provides an excellent base line in many types of research.

Of all the species of rats, the Norway rat is the undisputed champion. Cunning, resourceful, fierce and predatory, its numbers are limited only by the available food supply. Thanks to its incisor teeth, which in all rodents continue to grow throughout life, it has been known to gnaw its way through one-quarter inch steel to get food. Ordinary "rat proofing" is a relative term.

For a little over a hundred years the Norway rat has been propagated in the laboratory. However, in no way has it been domesticated; its vicious and aggressive nature commands the wholesome respect of those who must handle it. It occurred to Dr. Richter of Baltimore that 100 years in the history of the rat would be comparable to 5000 years in human experience, and that the Norway rat in captivity may have under gone changes that have significance in the development of man. Moreover, it is hard to find a group of humans who for 5000 years have had no contact with so-called civilization, while to compare the wild with the "domestic" Norway rat one needs only to set traps just outside the laboratory.

Richter[4] found the "domestic" and the wild strains as alike as peas in a pod in almost every particular, with these very significant exceptions: the anterior pituitary and the adrenal glands of the "domestic" rat were distinctly smaller, the adrenals being about one-third or one-fourth of the size of those of the wild Norway rat, and this reduced size of the adrenal was essentially a matter of less cortex.

Allergists have long known that, whereas the docile guinea pig can easily be sensitized to almost any antigen and can be killed in anaphylactic shock, all rats are hard to sensitize, and to produce anaphylactic shock in a rat one must first remove most of its adrenal tissue. Can it be that man, like the captive Norway rat, has had to fight less and less for his existence, and so has had less and less need for his "fight" and "stress" mechanism, with consequent shrinking in size of his adrenals? Can it be that the meek are inheriting the earth, and with it an increasing vulnerability to allergic disorders, arthritis and a variety of collagen diseases?

The rational use of steroid therapy requires a knowledge of some functions of the pituitary and adrenal glands, and of the behavior of these glands under certain conditions of disease and of unphysiological experience.

Some Functions of the Anterior Lobe of the Pituitary. The pituitary gland plays an important and indeed a dominant role in the endocrine system. It is, of course, subject to checks and balances by the hypothalamus and this in turn by higher cerebral centers; it is also responsive to feed-backs from other endocrine glands, but the fact remains that in the endocrine system it holds top rank in the chain of command. The anterior lobe produces several hormones, some of which stimulate other glands to perform their functions: the thyrotropic hormone causes the thyroid to secrete thyroxin; the follicle-stimulating hormone and the luteinizing hormone act on the gonads; the adrenocorticotropic hormone (ACTH) reacts upon the adrenal cortex. Partial or complete destruction of the pituitary gland results in symptoms referable to all its target organs. Therefore, myxedema, sterility and adrenal failure (Addison's disease, but without pigmentation) are seen in Simmond's disease, Sheehan's syndrome and progeria.

Some Functions of the Adrenal Cortex. The adrenal cortex, in response to stimulation by ACTH from the anterior pituitary, produces at least 28 steroid substances, the functions of only some of which are known with certainty. The outer layer, the *zona glomerulosa,* produces desoxycorticosterone (DOC) and is concerned with salt and water balance. The inner layer, the *zona reticulosa,* has to do with gonad function and is the source of estrogen, androgen and progesterone. The middle layer, the *zona fasciculata,* produces hydrocortisone, and probably aldosterone, and has an influence on the metabolism of carbohydrates and protein and probably on a variety of enzyme systems. *Excessive function* of the cortex (hypercorticism) produces Cushing's syndrome, the clinical picture of which is the same, whether due to a hypersecreting adrenal tumor, or secondary to excessive stimulation by ACTH, endogenous or administered. Destruction of the adrenals produces Addison's disease, and this type shows the familiar increased pigmentation of skin and mucous membranes.

Replacement Therapy. Thanks to a long series of researches, including the work of Swingle and Pfiffner and culminating in the discoveries of Hench and Kendall, it is now possible to give satisfactory replacement therapy to patients who have suffered loss of pituitary or adrenals by disease or by operation. In the case of the *anterior lobe of the pituitary,* such replacement could theoretically be accomplished by giving the several pituitary hormones. In practice this is not often possible since atrophy of the target organs renders any stimulation by these hormones impossible. Even when atrophy has not yet occurred, the pituitary hormones tend to lose their effectiveness through the development of antihormones. Treatment is, therefore, carried out by giving the hormones of the target organs: the thyroid, gonads and adrenals, as needed. In *Addison's disease,* the therapy depends upon the degree of adrenal destruction, beginning with increased salt intake, then desoxycorticosterone, and, if these fail and there is serious disturbance of nutrition, hydrocortisone.

The basic principle in all endocrine substitution therapy is to give the *least amount of hormone that will restore normal function.* A patient with total thyroid ablation needs ¾ mg. of thyroxin a day, the average normal output of the thyroid. The diabetic is given just enough insulin to cover his carbohydrate intake. Any excess of hormone would produce disease: hyperthyroidism, hyperinsulinism. Substitu-

tion therapy for pituitary or adrenal failure is no exception to this principle. While it is not yet possible to predict the extra amount of hormone a patient may need to meet certain stresses, it is now reasonably certain that the normal daily production of ACTH, and, therefore, the normal basic replacement need, is ¾ to 1 unit per day. Similarly, the daily hydrocortisone quota is from 12.5 to 25 mg.

What has been said thus far, disposes of all aspects of substitution therapy. It can be summed up in these words: substitution therapy replaces a hormone that a diseased or destroyed gland is unable to produce, and in an amount never greater than the daily deficit.

The most important corollaries to this statement are: first, that in none of the many other disorders in which steroid therapy has had any effect has there been shown to be any deficiency of normal output of ACTH or hydrocortisone: such treatment is in no sense replacement therapy; and *second*, the therapeutic effects of steroid therapy in these many disorders are based upon doses far beyond the amounts of these steroids normally present in the body, and, therefore, *potentially dangerous*.

Of basic importance in the use of steroid therapy is a knowledge of *the effect of the administration of an endocrine hormone upon the normal endocrine glands of the recipient*. For even the least amount has some effect. The *degree* of effect produced depends upon *how much* hormone is given, and *how long*. If a person is given a small dose of a hormone, his own gland will produce that much less, in order to maintain a normal state. Thus, if a man be given ¼ mg. of thyroxin a day, no thyrotoxicosis results, for his own thyroid will make only ½ mg., instead of the usual ¾ mg. If ¾ mg. be administered the thyroid will not produce any thyroxin. If this is continued for only a week or ten days, no structural change will occur in the thyroid; but if it be prolonged for weeks and months, then an atrophy of disuse will ensue: all this, if only ¾ mg. of thyroxin, the normal daily need of the body for maintaining a normal metabolism, be given.

When ACTH is given to a person, his own anterior lobe promptly produces less than it did. If the dose of ACTH exceeds *1 unit a day*, the man's own gland stops making ACTH entirely. For a week or 10 days, this does no obvious harm, but after that, atrophy begins.

If a person receives ACTH, and more than a unit a day, for a long time, say 3 months, then his own *anterior lobe* will have undergone obvious atrophy. During the same time, this excessive stimulus will cause the adrenals to hypertrophy, so that after 3 months they are 3 or 4 times the normal size.

Now if the ACTH be stopped, then the anterior pituitary will slowly resume its function, but even at 6 months after the stopping, *it will not yet have returned to its original size*. At the same time, the adrenal cortex, which now receives only the subnormal stimulus from its own pituitary monitor, rapidly atrophies, becoming in some weeks only a fraction of its normal size, and 6 months after the ACTH was stopped it has not yet returned to its original size and function.

If a person receives hydrocortisone in a 12 mg. daily dose or more, his own *anterior pituitary* no longer puts out any ACTH, and proceeds after 10 days to undergo atrophy which at three months is of marked degree. At the same time his *adrenal cortex* stops functioning and after 3 months has shrunken to a third or a quarter of

its original size. If now the hydrocortisone is stopped, then the anterior pituitary slowly resumes its function, but 6 months later it is still smaller and less efficient than it was to begin with. The adrenal cortex, after the stopping, slowly resumes its function, in response to the very subnormal ACTH stimulation from its own pituitary, and 6 months after the stoppage, it has not yet regained its original size and function.

In short, a person who has received ACTH or hydrocortisone in the doses mentioned for 3 months has incurred a deficiency of his own pituitary and adrenals that handicaps him for at least 9 months or a year. ACTH and hydrocortisone have been used as examples, but the same holds true for all the substances of the group. A common fallacy is the belief that prednisone and prednisolone do not have this effect, since only 5 mg. daily may be needed to keep a patient comfortable. But a 5-mg. dose of one of these substances is comparable not only in symptomatic effect but in production of glandular atrophy to 15 to 20 mg. of hydrocortisone. It is also fallacious to believe that the intermittent use of ACTH completely overcomes adrenal atrophy; pituitary atrophy will only be enhanced.

But what of the effect of very prolonged use: 2 or 3 years of such therapy? Here there is a dreary succession of disasters in patients, many of whom have been on treatment that long, whether justifiably or not. In these persons the degree of adrenal atrophy can be extreme. Such individuals are in essence man-made cases of Addison's disease. But whereas naturally occurring Addison's disease is a great rarity, there are thousands of cases of iatrogenic Addison's disease today. These differ in no way from the natural cases in their great vulnerability to any sudden stress. Any intercurrent infection is a most serious matter, because it can progress with such devastating speed that the patient perishes before help with more steroid and suitable antibiotic medication can be given. Even in hospital and under our very eyes this happens: the arthritic patient dies in 36 hours of a fulminating pneumonia or an acute appendicitis. Or a seemingly minor surgical procedure proves a fatal insult: as in a patient, also an arthritic, who developed a seemingly trifling infection of an olecranon bursa. It was incised in hospital and under local anesthesia. After 12 hours the patient felt fine, but in 12 hours more he died in acute adrenal failure. Or the asthmatic patient, subject of a Clinico-Pathologic Conference at the Philadelphia Meeting of the American College of Physicians, who ran out of her prescription for steroid one day and the next died in hospital in "status asthmaticus," precipitated by a respiratory infection. No one knows just how often these things happen, but they are all too frequent.

With an understanding of the essential endocrine interrelationships in the normal person, and a knowledge of the possible effects of steroid therapy upon the patient himself, one can now examine the *effects which such therapy can produce in the presence of various diseases.* As already mentioned, it is not a matter of substitution therapy. Rather is it a matter of dosage far in excess of normal requirements of steroid hormones. This deserves emphasis. The normal daily output of ACTH by the pituitary is probably not over one unit, yet we give up to 40 units a day. The adrenal glands produce a top amount of 25 mg. of hydrocortisone or less each day, but Rose has used up to 2000 mg. a day in asthma and Dubois gives as much as 4000 mg. a day in disseminated lupus.

Herein lies the tremendous power of the steroids both for good and for harm.

The effects of steroids can be good or bad. The good effects are essentially of three types: antiallergic, antiinflammatory and antirheumatic. The bad effects are of many kinds. Fortunately the good effects can be induced rather promptly as a rule, whereas the bad effects are mostly incident to prolonged use. Then it must be remembered that the good effects are purely symptomatic: the steroids cure nothing. If the cause of disease continues to be present, the symptoms will recur promptly when treatment is stopped. Then to obtain continued relief, the treatment must be resumed and continued for longer periods, with the increasing danger of unfavorable effects, to be risked only if threat to life, rarely to comfort alone, warrants. On the other hand, if the cause of disease be no longer present, or of limited duration, or if it be remediable or avoidable, then short-term treatment can be used with safety.

Therefore the indications for steroid therapy resolve themselves primarily in two groups: 1) Those for short-term use, that is, 10 days or less, and 2) those for long-term use.

Short-term steroid treatment. The indications for short-term treatment will now be cited.

1. Some of the most brilliant results of steroid therapy have been achieved in the treatment of *severe allergic reactions to known and avoidable allergens.* Please note the words severe, known and avoidable. Common examples are: *exfoliative dermatitis* from any drug that has been administered; *severe reactions to penicillin and other drugs; serum sickness; severe ivy poisoning* (it could be fatal) *trichinosis* (here the antigen, the protein from dying trichinella larvae, is limited in amount and duration of release); *Loeffler's syndrome* (but not tropical eosinophilia, in which a living, although unknown, agent is the probable cause, since one dose of an arsenical is curative); *the asthmatic who has to undergo an emergency surgical procedure* or a *bronchography while sensitive to the contrast medium; status asthmaticus* (but only when all other measures have been tried and failed; in the majority of such cases steroids are not necessary). *Malignant neutropenia* is primarily an allergic reaction, but during its course the patient is extremely vulnerable to any pathogens within or around him; therefore steroid therapy must be accompanied by a broad-spectrum antibiotic. The topical application of steroids in the conjunctival sac and the external ear, including postoperative use after fenestration procedures, may here be mentioned, since some of the indications are local allergic reactions. Such topical use does not involve systemic effects and therefore is harmless. It may require the added use of antibiotics, since infection is a frequent complication.

Topical use within the nose may be helpful to secure preoperative amelioration in some chronic allergic conditions such as polyposis, or while diagnostic studies are carried out to determine causes, which are then to be avoided or cared for by hyposensitization techniques. The injection of steroids intranasally in allergics must be looked upon as a questionable procedure, since sensitization to the steroid preparation may be so induced, especially in allergic individuals. Hay fever is not a proper indication for either topical or systemic steroid therapy: its proponents have been chiefly those who are inexpert in the specific management of pollinosis or who are unwilling to be so inconvenienced. One should not shoot sparrows with atomic warheads.

Since this presentation deals primarily with the allergic aspects of steroid therapy, other indications for short-term use will be dismissed with brief mention.

2. *Certain acute infections threatening life and caused by known organisms for which there are available effective antibiotics:* Waterhouse-Friderichsen syndrome in meningococcus infection, pneumonia, miliary tuberculosis and tuberculous meningitis, typhoid fever and acute peritonitis are notable examples. Here the combined use of steroid and the proper antibiotic is lifesaving. But it must be remembered that *the antiinflammatory effect of steroids masks the symptoms of infection.* As Salter put it, the steroids prove that it takes two to make a quarrel. The patient under steroids stops to fight his infection with fever and optimal local inflammatory reaction, but the pathogenic organism continues, unopposed, to harm and even to kill. Therefore steroids should never be used in infections for which no antibiotic is available, such as poliomyelitis, or in infections with a prolonged course, such as tuberculosis, leprosy and brucellosis. Malaria is made worse by steroids, and cerebral malaria may be precipitated in those with *P. falciparum* infection, a type which, therefore, precludes steroid therapy.

An important aspect of this inflammatory effect of steroids on infections is presented by the allergic patient who happens to have a coexisting infection or who may develop an intercurrent infection while on treatment. Examples of the former are sinusitis, bronchitis, and bronchiectasis. Here one must weigh the risk of flaring up the infection and be prepared to meet it with proper therapy. Patients on steroid therapy must be watched for intercurrent infection, and must be warned to report symptoms or significant exposure. Three deaths have recently been reported in children who while on steroid therapy developed chickenpox that then ran a fulminating course.

3. *A group of diseases and conditions mostly acute, mostly infectious but of unknown etiology,* have been found to react favorably to the antiinflammatory, and in one instance, the antirheumatic effect of steroids. They include acute rheumatic fever, erythema multiforme, lipoid nephrosis, thrombocytopenic and other purpuras, Bell's palsy, the myelitis following Pasteur treatment to prevent rabies, surgical shock, sprue refractory to other treatment, celiac disease, and as preoperative preparation in adrenal tumor. Gout is not a proper indication for the use of steroids: other measures are safer and more effective.

Before stating the indications for the *long-term use of steroid therapy,* one should consider its *long-term effects.* 1) The *atrophy* of the *anterior pituitary and adrenal glands* has already been mentioned. 2) Since long-term therapy involves the administration of steroids in excess of normal needs, there results some degree of *hypercorticism.* To be sure, the full-blown picture of Cushing's syndrome, with moon-face, acne, characteristic obesity, striae, hirsutism, hypertension and disordered gonad function, does not develop overnight, or even at all, if dosage be reduced as indicated. Or it may even be accepted as a justifiable risk under given circumstances. But there are many and less obvious effects of hypercorticism which must be considered and looked for. Since *hypertension* is a threat, the blood pressure must be regularly and frequently noted. *Edema* due to salt and water retention can early be detected by rapid gain in weight. *Mental symptoms* are frequent enough; insomnia, euphoria, at

times undue depression that may lead to suicide, changes in personality, and frank psychoses. Psychoses are particularly liable to occur in those who have ever had any previous psychotic trouble: indeed, such people should probably never be given steroid therapy. *Convulsions*, of unknown nature, although cerebral edema has been suspected, can develop suddenly and end fatally. *Glycosuria* is a common effect, that clears up when treatment is stopped. This does not mean that diabetics should not be given steroids, but they will need more insulin while on treatment. It also means that all patients should have regular examinations of the urine for sugar and should curb their carbohydrate intake accordingly. *Osteoporosis*, especially of the vertebrae, may lead to pathological fractures. *Peptic ulcer*, with bleeding and perforation, can occur. That cleft-palate can arise in the fetus while the mother is on steroid therapy has been observed in humans and also confirmed in animal experiments. *Allergy* to the steroid is a possibility. ACTH is a good antigen and some degree of sensitivity on second administration after a few weeks' interval has been observed. Indeed, a case of fatal anaphylactic shock has been reported, occurring when an intracutaneous skin test with too large a dose (4 units) was performed because of a history of allergy to ACTH. Fortunately the other steroids are poor antigens, so that reported sensitivities are infrequent, relatively mild, and related rather to parenteral than to oral administration. *Addiction* is a term that is used advisedly in patients who go into a panic at the mere suggestion of reduction or withdrawal of steroid dosage. *All the bad effects* of steroid therapy *occur* with far greater frequency *in those less and less able to cope with them: those over the age of 50.* Some of the bad effects of long-term steroid therapy are due to too high a dosage: the lowest dose that achieves results should be used; others are due to a too rapid withdrawal, resulting in acute adrenal deficiency: withdrawal must be slow, with a step-like reduction of dosage, and a temporary increase during stress or if symptoms develop. For at least a year after the end of prolonged steroid therapy, the patient who is to have an operation should be pretreated with hydrocortisone.

The contraindications to steroid therapy may now be summarized: all acute infections for which there is no available effective antibiotic; chronic infections, notably tuberculosis, leprosy, brucellosis; falciparum malaria; peptic ulcer; diverticulitis; chronic liver disease; severe hypertension; circulatory failure with edema; osteoporosis; severe diabetes; previous psychosis; and, in a relative degree, advanced years. It is unwise to give steroids during pregnancy.

The indications for the long-term use of steroid therapy can be summed up briefly as *those diseases for which there is no other help.* The abuse of such therapy results primarily from the fallacious interpretation of the words "*for which there is no other help.*" In practice they are changed to "*for which the physician knows nothing else to do.*"

In *allergy*, this refers especially to *asthma.* The short-term use of steroids in asthma has already been mentioned in status asthmaticus, when other measures have failed; in asthmatics who need an emergency operation, or who need a bronchography, although sensitive to lipiodol. To this may be added the somewhat longer use of steroid therapy in *severe* asthma, *after* the diagnostic survey has been completed, avoidable allergens have been eliminated and specific therapy for unavoidable allergens has been started: then

some steroid therapy may be used for a few weeks until the specific therapy begins to be effective. Finally, there are those cases in which all measures have failed and the patient is a virtual invalid. These have been referred to as cases of "*intractable asthma.*" Every allergist of long experience can think back upon a dozen or a score of such cases he has encountered over the years. But this writer looks askance on reports of the effects of steroid therapy in "164 cases of intractable asthma." Far too often, especially in general practice, such treatment is an unjustifiable short-cut around proper diagnosis and specific therapy which a physician is not equipped or trained to perform.

Of course, the patient feels well for a time on steroid therapy, but the relief is so often only temporary. Then when complications ensue, the blame is put upon the "new disease," not upon the treatment which caused it. Or the steroid loses its ability to relieve symptoms and the patient is now referred to an allergist.

Burrage *et al.*[1] reported an instructive case in point. A patient, aged 60, had developed asthma at 36, and for 24 years had wheezed his way through a rather miserable existence. At 59, in an attack of status asthmaticus, he got relief from a short course of cortisone. At 60, because of continued asthma, and in spite of an earlier history of duodenal ulcer and osteoporosis, he was placed on continued steroid therapy. For 8 months he did well. But 10 months after that he was dead. One might say, "A short life and a gay one." Short, but not gay, for at the end of 8 months the patient suffered pathological fractures of three vertebrae, with painful cord symptoms. Then followed 10 miserable months, punctuated by problems of edema, then ulcer recurrence requiring subtotal gastrectomy, and ending in "sudden" death while at stool. The necropsy, in addition to the vertebral fractures and pituitary and adrenal atrophic changes, showed a 2-day old, extensive, but asymptomatic and, therefore, unsuspected and untreated bronchopneumonia.

Nasal polyps can be caused to regress by the topical use of steroids as well as by internal administration. But, as Silcox[5] and others have pointed out, they recur when treatment is stopped, and surgical removal is usually needed to be followed by proper antiallergic measures. *Perennial allergic rhinitis* is relieved during steroid therapy, but the threat to the patient's adrenals makes unwise the long-term use which such cases would require. *Hyperplastic sinusitis*, since it has both an infectious and an allergic component, is not helped by steroids.

Severe generalized eczema may force one to the use of steroid therapy. Yet here one is reminded of the difficulties of allergic diagnosis by skin test in older patients. Those difficulties are increased by the effect of steroids in reducing skin reactivity. It is difficult to produce a hive, a skin reaction, in a patient who is also receiving the most potent anti-hive drugs, the steroids. It is not wise to use long-term steroid therapy for eczema in children for fear of serious damage to endocrine development. In eczema the local application of steroids has more justification, although absorption may not be inconsiderable, and in addition, there is a possibility of induced sensitization.

Beryllosis can threaten life and so steroid therapy is justified. The same is true of severe *purpura*. *Polyarteritis nodosa*, occurring as it does as often in asthmatics as in all other people put together, strongly suggests an allergic component. Steroid therapy has a beneficial effect, although temporary in most

cases. Occasionally, if started soon enough, and if a precipitating allergen such as a drug is known and avoided, it effects a cure.

Apart from allergy, there is a long list of *chronic diseases of unknown cause for which there is no other help* than symptomatic treatment with steroids. Among the *collagen* disorders, *scleroderma* and *dermatomyositis* may show temporary improvement. In *disseminated lupus,* the steroids give very gratifying relief, and may even prolong life a little: certainly they make bearable the remaining months or years of these patients. *Temporal arteritis,* although not a fatal disease, carries the risk of optic atrophy and blindness in half the cases, so that long-term steroid therapy is indicated in all cases.

In ophthalmologic practice, *sympathetic ophthalmia* in a remaining eye thoroughly justifies prolonged steroid therapy to prevent blindness. *Chronic relapsing uveitis* also is amenable to such treatment. *Retinitis with optic atrophy* has regressed from virtual blindness to effective vision as long as one year after the continued use of steroid therapy began.

In the digestive tract, remissions have been induced in *ulcerative colitis,* but here it is best to use the steroids last and for as short a time as possible. *Regional ileitis* has at times been favorably influenced.

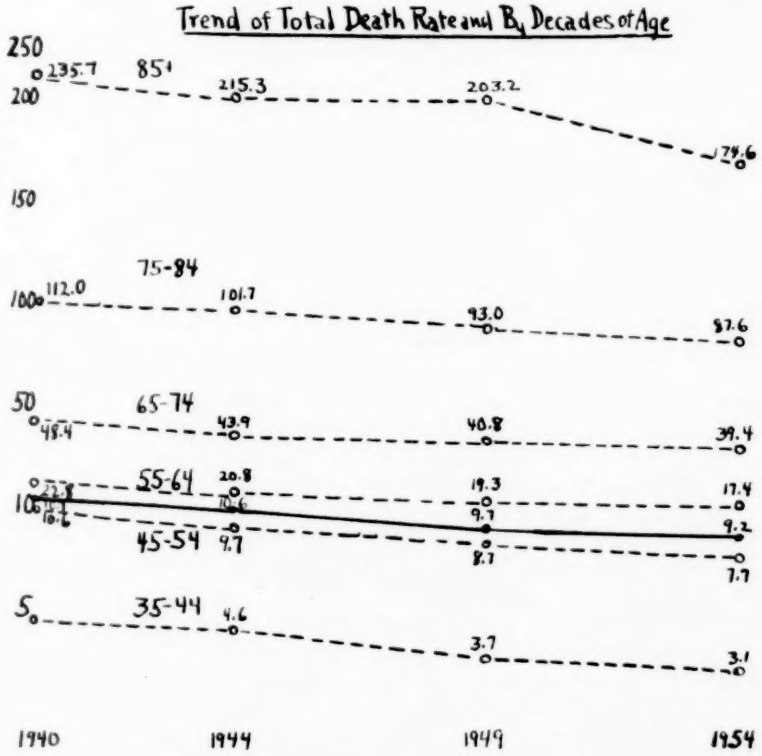

Fig. 1.—Note: Death Rates per 1,000 Population.

Pemphigus, severe *pulmonary involvement in sarcoidosis, splenic neutropenia, acquired hemolytic anemia* are conditions in which steroid therapy may give more or less relief. Even *acute leukemia* responds for a brief

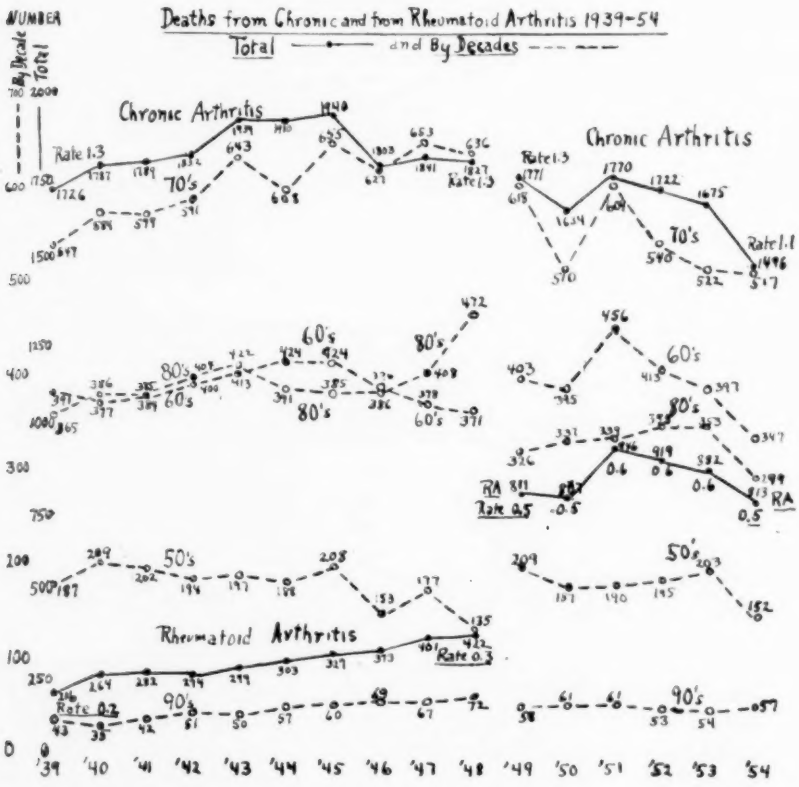

Fig. 2.—Note: Death Rates per 100,000 of Population. The solid line is the total death rate. Broken lines refer to age groups by decades.

time to such treatment, but neither the outcome nor the duration of illness is changed thereby.

The one nonallergic disease in which steroid therapy is abused as badly as it is in asthma is *rheumatoid arthritis,* and for a similar reason. Whereas the rheumatologist knows much that he can do to ameliorate this disease, and finds it necessary only under special circumstances and only in some patients to have final recourse to steroid therapy, the general practitioner uses the steroids first and alone. It was an example of such therapeutic abuse that prompted a search for the data that are now presented.

Last spring there died in his eighties an old friend of the writer. He had been troubled with rheumatoid arthritis for many years, but managed to get along in spite of it. Then steroid therapy was begun and in due course he died. The circumstances of his death

suggested a search of vital statistics for a hint as to the frequency of death from steroid therapy.

Figure 1 shows the total death rate and the death rates for certain age groups in the United States in 1940, 1944, 1949 and 1954. There is a steady fall in each category throughout the period.

Figure 2 shows the number of deaths in the United States from chronic arthritis (including rheumatoid arthritis), and from rheumatoid arthritis, between 1939 and 1954 inclusive. In addition there are plotted the deaths from chronic arthritis for certain age groups as well. (This was done because no figures for rheumatoid arthritis by age groups were available.) The curves are not drawn continuously, because in 1949 the sixth decennial revision of the list of causes of death was put into effect, so that figures before and after that date are not exactly comparable. In the same year, 1949, steroid therapy was introduced.

In the upper left hand side, before 1949, it will be seen that the incidence of *chronic arthritis* shows a rather level course: only in those in the seventies and the eighties is there an upward trend. Rheumatoid arthritis, on the other hand during this same presteroid era shows a steady upward trend, with a death rate of 0.2 per 100,000 of population in 1939 and 0.3 in 1948.

After 1949, the number of *chronic arthritis* deaths is no higher, except for high points in 1949 and 1951, and then there is a decline in total cases, and a fall in rate from a high of 1.5 in 1945 and 1.3 in 1949 to 1.1 in 1954. *Rheumatoid arthritis*, however, shows a definite peak in 1951, and the death rate that year was 0.6. However, it is again pointed out that figures after 1949 are not exactly comparable with those before because of the change in nomenclature. All that one can say, then, is that there is no significant change in the mortality of chronic arthritis, if anything a slight recent decline, while that from rheumatoid arthritis, which was rising slowly before 1949, has not continued to rise.

Now to return to the writer's deceased friend. It was mentioned he had had rheumatoid arthritis. But that was not the cause of death which appeared on his death certificate: it said "duodenal ulcer."

Figure 3 shows the data for deaths from *peptic ulcer*. Before 1949, there is a definite downward trend in the total number of deaths from ulcer; the downward trend of deaths in those under 60 more than offsets the upward trend in those over 60, especially in the sixties and seventies. After 1949 there is a steady increase each year in the total deaths, for although deaths in those under 50 have continued to fall, there is an increase in the fifties as well as in all groups over 60, especially again in the sixties and seventies. In this graph there is one curve that is drawn as a continuous line, because government statisticians have figured out a *corrected* rate for deaths before 1949 that is comparable with those after that. There is also a curve for uncorrected rates before 1949 in a broken line. It will be noted that the newer computation gives *lower* rates for the earlier period, so that the increases after 1949 are the more significant.

All of this still proves nothing, even though the increases of ulcer deaths in the fifties and the undue increase in the sixties are suggestive of a new cause or new causes operative in the production of ulcer. Thus, during war time, ulcers and ulcer deaths increase (the peak was in 1943), but it is the old who are more likely to succumb. After all, the old must die of something, and since deaths from infections

are fewer, there will be an increased mortality from other causes. But this is certain: ulcer is increasingly more dangerous in the aged, therefore a potential cause of ulcer, steroid therapy, must not be used lightly in those over 50.

The data for deaths from asthma tistics[7] points out that to compare the mortality figures for asthma before 1949 with those after 1948, the former must be multiplied by a factor of 1.6. Therefore a second set of death rate figures has been so determined and these are plotted as the one solid line

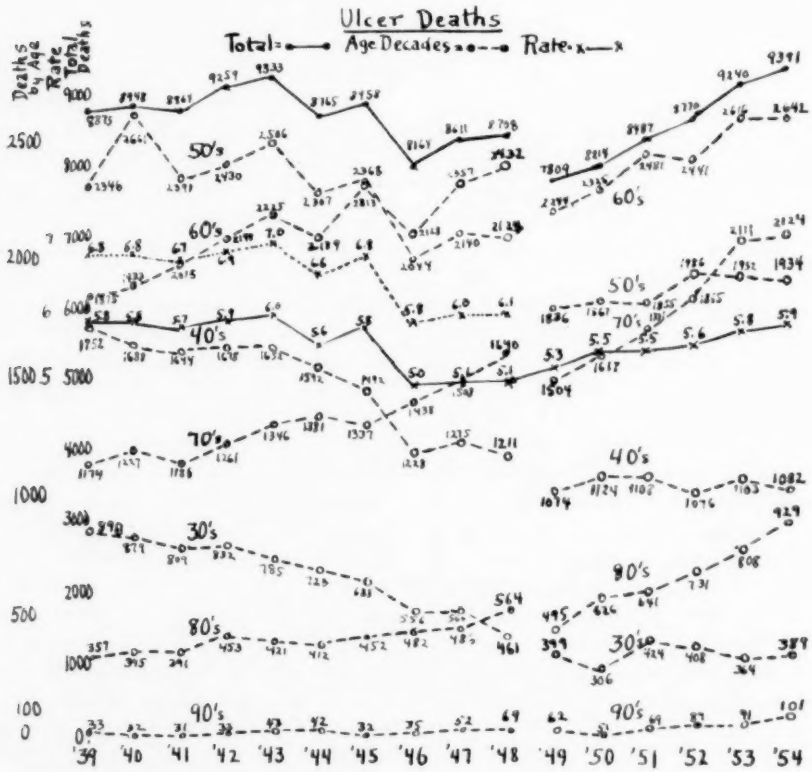

Fig. 3.—Note: Death Rates per 100,000 of Population.

are more revealing (Fig. 4). Before 1949, there is a slight upward trend in total deaths, notably in those over the age of 60. The death rate at the end of this earlier period is also slightly higher; 1.8, as compared with 1.6 at the beginning, but lower than the peak of 2.0 in 1943 and 1944. These earlier death rates are plotted on a broken line. The National Office of Vital Sta- that runs *continuously* through the graph.

The figures on deaths under age 30 (left upper quadrant) show no significant change before or after 1949. But after 1949 there is a sharp upswing at all ages over 40, with a peak in 1952 for all ages except those over 90, whose peak was reached a year earlier. This definitely suggests that in this pe-

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riod we seem to have eliminated a goodly share of our "intractable" asthmatics by means of steroid therapy. But the number of deaths from asthma and the death rate is still 25% higher in 1954 than in 1949 or in all of the period before 1949.

asthma and ulcer, are combined in Table 1. Although the figures before and after 1949 are not directly comparable, certain trends may be significant. There appears to be a definite decline in deaths due to chronic arthritis. But this may be more apparent

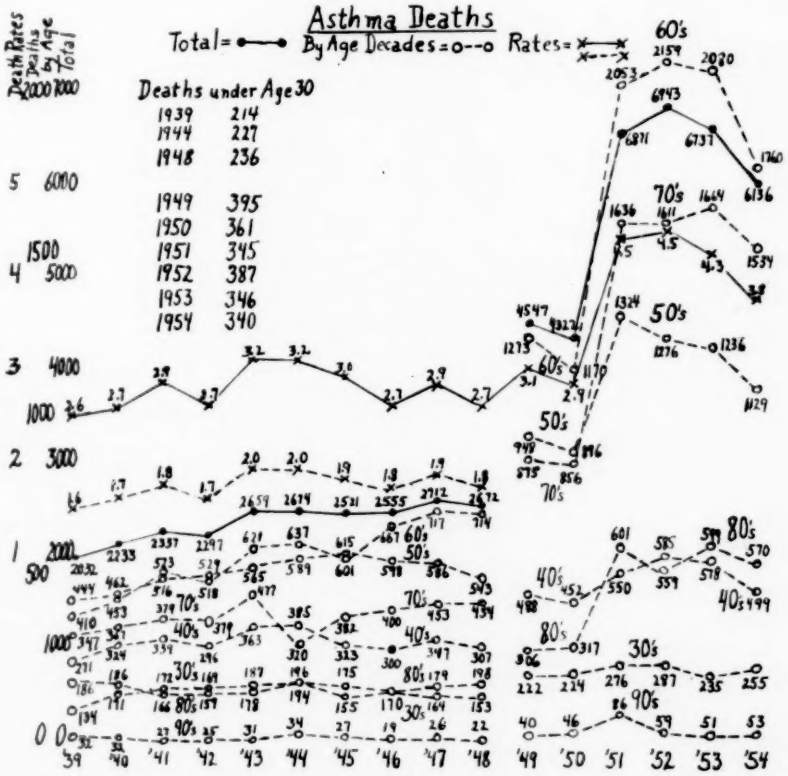

Fig. 4.—Note: Death Rates per 100,000 of Population. After the presentation of this lecture, word was received from the National Office of Vital Statistics[7] that to compare figures for asthma before 1949 with later ones, it is necessary to multiply the earlier figures by a factor of 1.6. The solid line which runs *continuously* through the graph plots the death rate figures which have been so calculated.

Final proof of the dangers of steroid therapy is unfortunately not to be obtained in vital statistics. No deaths are listed as due to steroids. Doctors' mistakes are still buried, not reported.

The death rates by age groups for all three conditions: chronic arthritis, than real, since some of the increase in ulcer deaths in older persons may represent the results of steroid therapy of arthritis. The increased death rate in older asthmatics seems clearly to implicate such treatment. Prolonged steroid therapy in arthritics and asth-

matics over 50 should not be undertaken except upon truly urgent indications. The high and rising death rates from asthma and from ulcer in those over 60 (underlined figures) call for serious consideration by all physicians.

In October, 1956, Hiddlestone[3] stressed to New Zealand physicians the growing importance of asthma, and cited the rising number of deaths from this cause and the death rates. The

A final word about the newer steroids, *prednisone and prednisolone.* Much has been written about the advantages which these substances have in certain respects over other steroids. Reference is made to only one excellent article by Spies, García, Díaz, López, Reboredo and Suárez[6] which appeared in October, 1955, in the Journal of the American Medical Association. On the basis of a large number of patients with various diseases treated

TABLE 1.—CERTAIN DEATH RATES PER 100,000 POPULATION BY AGE GROUPS IN 1940, 1944, 1949 AND 1954

	Chronic Arthritis				*Asthma*				*Ulcer*				
Age	*1940*	*1944*	*1949*	*1954*	*1940*	*1944*	*1949*	*1954*	*Age*	*1940*	*1944*	*1949*	*1954*
20's	<0.2	0.1	<0.1	<0.1	0.4	0.4	0.5	0.5	25–34	2.3	2.0	0.9	0.8
30's	0.3	0.24	0.16	0.1	0.8	1.0	1.0	1.1	35–44	5.9	5.1	3.5	3.2
40's	0.5	0.5	0.4	0.3	2.0	2.2	2.5	2.4	45–54	11.6	10.2	8.4	8.1
50's	1.5	1.4	1.4	0.9	3.6	4.3	6.3	6.9	55–64	17.6	18.4	16.3	15.9
60's	4.5	4.7	2.7	2.9	5.4	7.0	12.9	*14.9*	65–74	22.2	22.0	25.3	*28.1*
70's	13.6	12.3	10.7	7.8	8.5	6.5	15.3	*23.6*	75–84	29.6	23.7	31.6	*42.2*
80's	29.7	24.4	18.1	10.3	14.3	12.2	17.0	*19.6*	85+	27.9	——	37.3	*51.8*
90's	——	——	——	——	——	——	——	——					

TABLE 2.—TOTAL DEATHS AND DEATH RATES FOR ASTHMA IN NEW ZEALAND (HIDDLESTONE)

Year	*'39*	*'40*	*'41*	*'42*	*'43*	*'44*	*'45*	*'46*	*'47*	*'48*	*'49*	*'50*	*'51*	*'52*	*'53*	*'54*
Deaths:	28	24	35	47	39	35	53	30	54	44	58	140	159	208	179	189
Rate (per 100,000 population)	1.71	1.46	2.14	2.86	2.38	2.11	3.12	1.70	2.99	2.38	3.08	7.28	8.16	10.42	8.73	6.63

figures are strikingly similar to our own, with a sharp increase over 1949, a peak in 1952 and a slight fall-off thereafter. Moreover, the age group pattern in the year 1952 shows that of the total of 208 deaths, 61 occurred in the sixties, 50 in the seventies, 40 in the fifties, and 21 in the forties, again as with us, maximal in the sixties. He was, however, not concerned with any possible unfavorable effect of steroids. Indeed, he pointed out that infection plays a dominant role in death from status asthmaticus and advises 24 hours' treatment with antibiotics and then the additional use of cortisone or hydrocortisone.

with these substances, the authors conclude that they possess the same antiallergic, antiinflammatory and antirheumatic properties as cortisone and hydrocortisone, and, in addition, they do not cause retention of sodium and water. The latter quality permits their use in patients with circulatory conditions in which any fluid retention would be seriously embarrassing. But they emphasized that these drugs produced the same side effects and in the same frequence with therapeutically effective doses as do cortisone and hydrocortisone. Indeed, they cautioned that patients on these drugs must be watched more closely, since damage

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could ensue more insidiously in the absence of the red flag of edema. They also counseled that these drugs be used intermittently rather than continuously, and that other measures be used to the utmost of their effectiveness in preference to the steroids.

What happened to this good advice?

Everyone who publishes an article in a medical journal wonders what his readers think of it. He can gauge its value in some degree by the requests for reprints which he receives. But he is sure the article is good if one of the journals distributed gratuitously to all physicians (the advertisements pay the cost) selects the article for republication in abstract. And so in January of 1956 "*Medicine*" published a good resumé of the article by Spies and his colleagues under the title "Therapy with Recent Corticosteroids."

But one has really arrived if his article gains the attention of *Reader's Digest*. So in December, 1955, this paper received high approval in an article by DeKruif. Furthermore, the foreign-language editions of that publication also took it up. As the writer reads the Spanish edition, he encountered it in the March number of *Selecciones del Readers Digest*, but with this title: *Superaspirina para los Artríticos:* superaspirin for arthritics.

Little wonder that there is an increasing tendency for general practitioners to treat their patients with asthma or arthritis or hay fever with these drugs and without proper diagnosis or careful follow-up. When treatment fails or complications arise, the patient is turned over to the specialist. But what of the damage that has been done in the meantime?

Some people do worry about them. Here is a quotation from a letter which Armour Laboratories sent early in 1956 to all physicians:

"Dear Doctor:

"Prednisone and prednisolone were originally introduced as safer, more potent analogues of cortisone and hydrocortisone. The promise of greater safety was responsible for the enthusiastic acceptance of the new steroids and has led to a remarkable increase in the number of steroid users. While the new steroids are a valuable therapeutic addition, our concern deals with a false sense of security which appears to prevail among physicians who had previously shied away from corticoid therapy. . . .

"It appears to us from surveys that a great many physicians evaluate safety in steroid therapy essentially in terms of side actions, such as sodium retention and weight gain, hypertensive effects, decrease in sugar tolerance, moonface, etc. Yet these side actions hardly deserve being called dangerous because of their gradual, readily noticeable appearance and their reversibility on dosage reduction or hormone withdrawal. Indeed, these side effects, particularly weight gain, are really early warning signals of beginning overdosage.

"One effect, however, adrenal cortical suppression and atrophy, is not an overdosage effect, but the unavoidable accompaniment of any corticoid therapy, whether cortisone, hydrocortisone, prednisone or prednisolone is employed.

"What appears to be ignored are these three facts: 1) that the new steroids, because they are more potent, are also more potent in inducing side effects and adrenal cortical atrophy; 2) that therapeutically equivalent doses of old and new steroids have the same undesirable effects, ... 3) that absence of water and sodium retention implies a greater rather than a lessened risk of exposing the patient to the various other side effects."

Nevertheless, other drug manufacturers are compounding the felony by purveying preparations containing steroids and aspirin and antihistaminics. Indeed some are applying for permits to sell steroids over the drug store counter without prescription, and that, of course, means without diagnosis or medical supervision.

There is the story. It contains food for thought for all physicians, for sooner or later most of them come to grips with the problems it presents. Their solution involves first, a knowledge and understanding of the indications for steroid therapy, of the other treatment measures that must be tried in various diseases before resorting to steroid therapy, and of the side-effects and dangers that such therapy may entail; and second, the wisdom to decide when to take those calculated risks. But above and beyond these considerations lies an ethical principle: *Primum non nocere*. What was enjoined in the Hippocratic oath is binding today upon the physician: that he shall not knowingly do his patient any harm.

Summary. The indications, contraindications and dangers of steroid therapy are reviewed. Its proper use rests upon an appreciation of these facts: 1) that steroid therapy in diseases other than destruction of pituitary or adrenals is not *replacement* therapy providing normal daily hormone needs but *symptomatic* (not curative) treatment which owes its effects to doses far exceeding normal needs and, therefore, leads to commensurate degrees of hypercorticism; 2) that the administration of any corticosteroids results in diminished output of hydrocortisone by the adrenals, and, if administration is prolonged, in adrenal atrophy; 3) that such atrophy, upon sudden cessation of treatment or suddenly increased stress (infection, operation) is responsible for acute absolute or relative adrenal insufficiency; 4) that short-term steroid therapy, for example of serious acute allergic states due to known and avoidable causes, or of rheumatic fever, is highly effective and safe, and, in combination with the proper antibiotic, may be lifesaving in overwhelming infections due to known bacteria against which the antibiotic is effective; 5) that prolonged therapy of chronic allergic and of other diseases of unknown etiology involves risks that must be justified by attendant major threats: for example, to sight, or to life itself. Attention is called to mortality statistics in the United States which show a sharp upswing in deaths from asthma in those over 50 since the introduction of steroid therapy and probably as a result of its use. A rising incidence of ulcer deaths in older patients prompts greater caution in the use of so potent an ulcerogenic group of substances in those over 50. *Primum non nocere* is still a binding principle of medical ethics.

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SUMMARIO IN INTERLINGUA

Le Uso e le Abuso de Therapia Steroide, Notabilemente in Disordines Allergic

Es presentate un revista del indicationes, contraindicationes, e periculos de therapia steroide. Su uso convenibile depende del appreciation del sequente factos: (1) Que le therapia steroide in casos altere que casos de destruction del glandulas pituitari o adrenal non es un therapia de *reimplaciamento* que debe satisfacer normal requirimentos diurne de hormones sed un tractamento *symptomatic* (non curative) que produce su effectos gratias a doses excedente per multo le requirimentos normal e que, per consequente, resulta in commensurate grados de hypercorticismo; (2) que le administration de omne corticosteroide resulta in un diminuite production de hydrocortisona in le glandulas adrenal e, si le administration es continuate durante longe periodos de tempore, in un atrophia adrenal; (3) que un tal atrophia es responsabile pro le acute absolute o relative insufficientia adrenal que eveni post le subite cessation del tractamento o un subite augmento de stress (infection, operation); (4) que un therapia steroide a breve duration, per exemplo in serie acute statos allergic ab cognoscite e evitabile causas o in febre rheumatic, es multo efficace e secur e pote, in combination con le appropriate antibiotico, salvar le vita del patiente in infectiones invasive per cognoscite bacterios contra le quales le antibiotico es efficace; e (5) que le prolongate tractamento steroide de chronic morbos allergic e de altere morbos de etiologias non cognoscite constitue un risco que non pote esser justificate excepte in le presentia simultanee de major periculos pro (per exemplo) le senso visual o le vita mesme. Es signalate que le statisticas del mortalitate in le Statos Unite revela un acute augmento de mortes ab asthma in patientes de plus que 50 annos de etate depost le introduction e probabilemente como resultato del therapia steroide. Le crescente incidentia de mortes ab ulcere in patientes de etates plus avantiate suggere le necessitate de un plus caute circumspection in le uso de un si potentemente ulcerogene gruppo de substantias in personas de plus que 50 annos. "Primo non nocer" remane un principio obligatori del ethica medical.

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PROGRESS
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MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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TUBERCULOSIS OF THE LARYNX

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THE purpose of this review is to portray the present status of laryngeal tuberculosis, as expressed in the American and English literature. Foreign language summaries were obtained in Excerpta Medica, and much information derived from the excellent bibliographic survey by Wilson and Stern[71]. The number of articles dealing with laryngeal tuberculosis and antimicrobial therapy is so great that not all could be included. However, the publications described in this review were included on the basis of chronological priority, because of the large number of patients studied, or because they presented some original aspect of the disease.

The discussion of laryngeal tuberculosis in this review is approached from three points of view: 1) etiology; 2) pathology; and 3) treatment. Most articles deal with incidence, etiology, and gross pathology before discussing the results of treatment. Also, many articles discuss the toxic effects of new drugs, an aspect that has not been included in this review.

There have been a number of detailed studies of the incidence of laryngeal involvement in pulmonary tuberculosis. The route of infection of the larynx, whether hematogenous or local invasion, has been frequently discussed, the gross and microscopic pathology carefully studied, and the symptoms and prognosis fully described. Steady progress has been made in each of these aspects of the disease. Most articles, however, are concerned chiefly with the results of antimicrobial therapy, and it is in this field that distinct advances have been achieved. The past 10 years have witnessed the introduction of streptomycin as well

as a number of other drugs, equally effective against tuberculosis.

Etiology. Auerbach[3] reported the results of necropsies performed on 811 patients dying of pulmonary tuberculosis. In 304, or 37.5%, patients evidence of laryngeal tuberculosis was discovered. Piechaud[54] stated that one-third of all pulmonary cases have involvement of the larynx. Fenton[19] quoted Fetterolf as finding at necropsy that 83% of pulmonary patients had laryngeal disease but that 2.5% is the approximate figure at present. O'Keefe[49] found that 16.6% of pulmonary patients have tuberculous laryngitis. Vadala[63] found only 1.2% in 4000 patients with pulmonary disease.

Shikano[59] found 13% of pulmonary patients have laryngeal complications, the percentage being much higher in patients with atrophic rhinitis. Dupont[16] found 126 cases among 1,100 males with pulmonary tuberculosis. Ginader and Rickmann[25] diagnosed 28 cases among 500 patients with lung disease.

Ormerod[50] described 30 years experience with tuberculosis. In 1933, 25% of pulmonary patients developed laryngitis; by 1949, the figure had been reduced to 2.5%.

DePriest[15], covering 20 years experience with 5000 patients found 648, or 13%, had laryngeal complication. Lell[33] listed 40% of females and 44% of male patients as developing laryngitis. He explains the high incidence as being due to his inclusion of incipient changes which may have not been specific in origin. Schwarzbart[58] states that the incidence of laryngeal tuberculosis declined from 40% in 1920 to 3% in 1950, this improvement coming on without benefit of antimicrobial therapy.

Looper[35] reported observations on laryngeal tuberculosis over a period of 28 years. From 1923 to 1928, of 3,227 pulmonary patients 500, or 15.5%, had laryngitis. From 1938 to 1948, of 2,770 patients only 214, or 7.7%, developed complications in the larynx.

Tavani[61] described 13 cases of tuberculous laryngitis in children, and discussed the reason for its rare occurrence. D'Angelo[13] found 7 cases of bovine infection of the larynx in children and adults.

Thus there is seen to be a wide variation in the figures for the incidence of laryngeal involvement in pulmonary tuberculosis. This may be explained by the different racial and economic levels in various countries, and on the criteria used for the diagnosis of specific laryngitis. There is general agreement among all observers on the steady decline in incidence over the years. This has been accomplished without antimicrobial therapy, and may be ascribed to earlier diagnosis, better general care of pulmonary tuberculosis, and the use of collapse and extirpative therapy. A figure between 5% to 10% is believed to represent the incidence of laryngeal tuberculosis in this country during the years immediately before the introduction of streptomycin.

Auerbach[3] is convinced that tubercle bacilli invade the larynx locally through the mucous glands, and that the hematogenous route is rare. Danowski[14] believes the bacilli invade the mucosa through microscopic erosions. Piechaud[54], Milot[40] and Jaros[29] believe in local invasion. Tavani[61] says that the hematogenous route is more common in children. In adults, direct invasion by bacilli from the sputum is more common. Morussi[47] states that the larynx may be invaded by either route. The larynx may be assumed to be involved via the blood stream in miliary tuberculosis, in the mixed miliary and nodular form, and in the clinically fulminating types, with a sudden onset and a rapidly fatal course.

It would seem that in spite of these careful investigations it has not been proved definitely by which route the larynx is invaded. The evidence indicates that either route may be followed, with local invasion by the bacilli-laden sputum more common in adults. There is general agreement that by whatever path, the larynx becomes involved only secondarily to pulmonary disease, which is usually far advanced and bilateral. The appearance of laryngeal disease indicates decreased resistance on the part of the patient to his pulmonary tuberculosis.

Pathology. Articles dealing with tuberculosis of the larynx for the most part ignore a standard method of classification of the disease. Three general methods of classification are undertaken: 1) pathological, based on the chief gross alteration, such as infiltrative, ulcerative, exudative, edematous, granulation or tuberculoma; 2) anatomical, such as cordal, epiglottis, posterior commissure, arytenoid, and others; 3) degree of involvement, such as incipient, moderate and extensive. Each method of classification has advantages as well as disadvantages. The pathological method was most commonly described and probably best conveys a picture of the appearance of the larynx. However, usually more than one gross pathological alteration is present. A better picture may be obtained by combining all three, namely, extensive ulceration of both true cords, large tuberculoma of the posterior commissure, and diffuse edema of the right arytenoid and aryepiglottic fold. In this connection, the classification of carcinoma has become more standardized. It is more difficult to classify an inflammatory disease of the larynx, which tends to be diffuse, than a tumor.

Auerbach[3] studied 304 larynges with tuberculosis. He states that the basic gross pathologic lesion is the ulcer, with the vocal cords the most common site. A widespread belief that the posterior commissure is the most frequent site has been attributed to infiltrative alterations that often were not tuberculous.

Auerbach[3] also studied the 304 larynges histologically. He found that bacilli enter through the ducts of mucous glands rather than through intact epithelium. Tuberculous foci are set up, consisting of epitheloid cells, giant cells, fibroblasts and lymphocytes, arranged concentrically. The larger foci have central areas of caseation. Such areas do not lead to ulceration, unless the process extends to involve the overlying mucosa.

Danowski[14] studied the histopathology of 15 tuberculous larynges. He found that the bacilli penetrate the mucosa through microscopic erosions. The laryngeal cartilages were involved in 13 instances.

Shinozuki[60] described the histopathology present in 16 patients. He attributed the perivascular infiltration to tubular invasion rather than to hematogenous infection. Eschweiler[17] made a most valuable contribution to the microscopic pathology of laryngeal tuberculosis. In a group of 24 patients he studied various laryngeal components, correlating their involvement with symptoms. He found that the muscles and joints are usually spared, even in extensive laryngeal disease. (This offers an anatomical basis for the clinical observation that fixation of the cords does not usually occur, even in marked laryngeal tuberculosis. This is important in differential diagnosis, since in carcinoma early extracordal lesions cause fixation.)

Johansen[30] discussed the relation of contact ulcers to tuberculosis. Of 19 patients with contact ulcers, 14 were

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shown at necropsy to be due to tuberculosis.

A number of important studies of the histopathology of healing following antimicrobial therapy are discussed under the heading of treatment.

The preceding articles provide important contributions to knowledge of the histopathology of laryngeal tuberculosis. In general they tend to confirm previously established concepts, rather than offering new or controversial material.

Treatment. In October, 1946, at the annual meeting of the American Academy of Ophthalmology and Otolaryngology, Dr. Frederick Figi[21] presented a paper on "The Treatment of Tuberculosis of the Larynx with Streptomycin." Photographs revealed the appearance of the larynx before treatment, and the remarkably rapid healing that occurred after use of streptomycin. This paper has come to be regarded as marking the beginning of the era of antimicrobial therapy in laryngeal tuberculosis. (Actually, Dr. Figi reported on the results of streptomycin in one patient with laryngeal tuberculosis a few months earlier.)

Other papers reporting on the beneficial action of streptomycin appeared rapidly. No attempt is made to present them in exact chronological order. Bogen[7] and Black[6] reported in November, 1947, on results obtained with 34 patients. They used from 0.5 to 2 gm. of streptomycin intramuscularly and 0.5 gm. by aerosol inhalation. Of the 34 patients thus treated, 13 were healed and 17 improved, while 4 were worse.

Withers[72] treated 12 patients with streptomycin, 10 being completely healed and 2 improved. Gilbert, Aronoff and Rosen[23] observed the effects of streptomycin on 20 patients; 14 were healed, 4 almost healed, and 2 improved. Arnaud and Alcalays[2] had a large series of 85 patients, 67 being given intramuscular streptomycin, and 18 receiving the drug by aerosolization alone. Of those given parenteral therapy, 23 were completely healed, 33 healed with some residual changes, 6 were unchanged and 2 became worse. Those receiving aerosolization alone obtained poor results. Leroux[37] found that streptomycin administered by aerosolization had no effect on 36 patients. When streptomycin was given in dosages of 1 gm. intramuscularly for 4 to 6 weeks there was rapid improvement. The slight effect of streptomycin given by aerosolization as compared to the intramuscular route was also observed by Bernard and Arnaud[4], Vadala[63], Pfuetze and Ashe[52], Fanconi and Löffler[18], Bunn[9], Cody[11], and others. After these publications aerosol therapy was gradually abandoned by most investigators.

Wallner *et al.*[67] reported on the results of streptomycin in 52 patients with laryngeal tuberculosis; 25 were healed, 18 had moderate improvement, 5 had slight benefit, 2 were unchanged, and 2 became worse. Photographs illustrated the appearance of the larynx before and after treatment in 6 of the patients.

Large series of patients with tuberculous laryngitis treated by streptomycin with marked benefit in most instances were reported by observers in Veterans Administration Hospitals[41, 42, 43, 44, 45, 46] by Ormerod[50], DePriest[15], Ferreri[20], Zanzucchi[74], Quesda[55], Milot[40], Dupont[16], O'Keefe[49], McKenzie[38], Rossi and Fasano[56], Lieberman and Lell[34] and Lell[33].

Calvet, Coll and Malhiac[10] discussed the late appearance of the larynx following the use of streptomycin as well as the question of recurrence. No recurrence was found in a larynx that had been completely healed. When recurrences develop it is at the site of

the original lesion where there were residual alterations after treatment.

The conclusions from these papers on the effect of streptomycin in laryngeal tuberculosis may be summarized as follows: Streptomycin has a marked beneficial effect and is much superior to medicaments previously available. There is prompt and complete relief of pain, and usually great improvement in hoarseness. Objective evidence of healing occurs in most instances, being complete in about 50% of patients. This beneficial effect on the larynx occurred in spite of little or no improvement in the pulmonary disease state. The improvement in the larynx was usually maintained even when the general condition deteriorated. Recurrences in the larynx were not common. The one factor limiting the value of the drug was the development of organism resistance, so that after 60 days further therapy was of little benefit.

The success achieved by streptomycin in the treatment of tuberculosis has stimulated the search for similar drugs. Para-aminosalicylic acid (PAS) was synethesized by Lehman of Sweden especially for its bacteriostatic action against the tubercle bacillus. It is given orally, 12 gm. per day in four divided doses, or as the sodium salt, 16 gm. per day. Gastrointestinal irritation is common, but true toxic effects are rare and usually not serious.

One of the earlier reports on the effect of PAS used alone in the treatment of laryngeal tuberculosis was made by Nielsen and Vallintin[48] in 1950. Of 15 patients treated by dosages of 12 to 14 gm. per day, all responded. Cristiani and Pifferi[12] treated 24 cases, comparing the effect of PAS alone to PAS combined with streptomycin. The results were about the same in the two groups. (Certainly this is not the experience of most observers, including this writer.) Zanzucchi[75] treated 25 cases of tuberculous laryngitis with PAS alone with improvement occurring in certain types. Gilbert and Aronoff[24] treated 21 patients with PAS alone; 13 had primary healing, 5 improved, and 3 were failures. Wallner *et al.*[67] reported on 70 patients receiving streptomycin, PAS, or both. PAS was not as rapidly effective as streptomycin, but could be used in cases where streptomycin had been used previously with the development of resistant organisms. Further studies determined that used together, as combined therapy, PAS seemed to delay the emergence of organisms resistant to streptomycin, thus allowing its effective use to be prolonged. Combined therapy gave better clinical results than when either drug was used separately. Large series treated by combined therapy with excellent results were published by Lehman[32], Vadala[64], Gilbert and Aronoff[24], Lumio[36] and Wallner[68].

Further studies and clinical experience have demonstrated that PAS by itself is a comparatively weak drug against tuberculosis, far inferior to streptomycin or isonicotinic acid. However, it does possess the important ability to delay the development of strains of organisms resistant to one of the other drugs. Hence it is used in most treatment regimens today, combined with streptomycin or isonicotinic acid or both. Many other drugs have been introduced for the treatment of tuberculosis. Some are so new that their clinical value has not been determined. Others have shown effectiveness, but not in sufficient degree to displace the more effective well-established agents. One that received wide attention in the literature, especially abroad, was Thiosemicarbarzone (Tibione, Conteben, tbl). It was introduced by Domagk of Germany, generally credited as the discoverer of the sulfonamides. This drug is reported

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as having marked beneficial action in tuberculosis, including the extrapulmonary and laryngeal forms. Most articles on its use are from Germany, the European continent, and Japan.

Stutz reported on 41 patients with laryngeal tuberculosis treated with tibione. The dose was 25 to 50 mg. daily. There was prompt relief of pain, and objective healing occurred in one to four weeks. Thirty-two patients, or 78% were considered cured. A number of toxic reactions were encountered. Lederer and Gulich[31] treated 83 patients with severe tuberculous laryngitis with Conteben. Dysphagia disappeared in one to five days; 76% were symptom free, 18% were improved, and 6% unchanged. Good results were also reported with tbl by Wolf[73], Pagliarini[51], Schurman and Radenbach[57] and Goto *et al.*[26]. Gilbert and Aronoff[24] treated 20 cases with tibione. Only 5 patients were healed, 11 improved, and 4 were failures. The toxic effects observed were severe, and far more frequent than reported by the German investigators. Wallner's results at the Chicago Municipal Tuberculosis Sanitarium were similar. The drug appeared to have a far weaker effect than either streptomycin or PAS, while toxic reactions were frequent and severe.

Another recently introduced drug has become important in the chemotherapy of tuberculosis. Isoniazid was introduced for clinical trial in 1951. Its value in tuberculosis was quickly established and it has become almost as useful as streptomycin.

There have been comparatively few papers published on the use of isonicotinic acid alone in tuberculous laryngitis. This may be explained by its recent introduction and also because of the fewer number of cases of laryngeal disease as the result of prolonged therapy by drugs introduced at an earlier date.

Piasecki[53] treated 60 cases of tuberculous laryngitis with isoniazid alone, as well as in combination. While isoniazid was found beneficial in most instances, combined therapy gave the best results. Gardenghi[22] reported on the clinical results in 10 patients who were given isonicotinic acid 150 to 200 mg. t.i.d.; 6 recovered, 2 were considerably improved, and there were 2 failures. The drug is usually combined with PAS or streptomycin, so that there is seldom opportunity to observe its effect alone. Where this was possible (Wallner, Thompson and Lichtenstein[70]) the results were comparable to streptomycin.

Arnaud and Alcalays[2] studied the cicatricial stenosis of the larynx following the use of streptomycin for tuberculous laryngitis. They concluded that this condition is more common now than before the introduction of chemotherapy. They believe that this may be due to the fact that patients formerly died before developing cicatrization of the laryngeal lesions. (We have seen a number of instances of cicatricial stenosis in our series of patients, some of whom required tracheotomy. One patient had complete adhesion of the true cords along the entire length, following the healing of ulceration.) Studies on the histopathologic effects produced by chemotherapy in laryngeal tuberculosis have been described by Tavani and Cherubino[62], Greven[28], Wallner, Thompson and Lichtenstein[69, 70]. These studies reveal that the histologic process may persist after gross healing seems complete. The sequence of events includes disappearance of tubercle bacilli, diminution of inflammation, disappearance of tubercles, and, finally, replacement of necrotic material by connective tissue.

Summary. The present status of laryngeal tuberculosis, as determined by a study of the literature published

during the past 10 years, may be summarized as follows: The incidence of laryngeal involvement in pulmonary tuberculosis was from 5 to 10% just before the introduction of streptomycin. It is much less frequent today. The larynx almost never becomes involved among patients who receive prolonged chemotherapy. As a result, laryngitis is not seen in patients once they are started on treatment. Most new cases of laryngeal tuberculosis occur in patients who have not been previously diagnosed or have not had treatment.

Three or more drugs are now available which are capable of curing or, at least, greatly ameliorating tuberculous laryngitis. Pain is completely relieved in all instances, while hoarseness is usually greatly improved. Complete anatomical healing occurs in about 50% of treated patients; in the others, there is marked improvement, although accompanied by hyperemia, infiltration, or distortion due to scarring or loss of substance. Healing occurs independently of corresponding improvement in the primary disease in the chest.

The prognosis of laryngeal tuberculosis has been improved so greatly that it may be stated that after proper therapy, the larynx is no longer a problem, nor is this structure a menace to the patients' recovery from tuberculosis.

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DERMATOLOGY AND SYPHILOLOGY

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SOME ASPECTS OF CUTANEOUS MALIGNANCY

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IN 1946 the general subject of tumors of the skin was reviewed in this Journal[11] and in 1955 malignant melanoma of the skin was brought up-to-date[13]. In addition, Kochs[60] has covered the subject of cutaneous tumors in a broad way and Ervin Epstein[37] has reviewed sarcoma involving the skin. In this presentation, certain other aspects of some of the malignant processes involving the skin will be discussed, namely: metastases of the skin from internal malignant disease (specific); cutaneous manifestations of internal malignancy (nonspecific); and cutaneous malignancy developing in some diseases of the skin. Although data contained in the earlier general discussion of tumors of the skin will be referred to, the intent is only to relate these matters to newer developments in the respective fields.

MULTIPLE MALIGNANT GROWTHS. In our 1946 review it was apparent from the available literature that cancer of the skin was not protection against the development of cancer elsewhere. As with other types of cancer, cancer of the skin is associated with a greater number of multiple cancers than would be expected on the basis of chance. More recently, Lombard, Levin and Warren[69] reaffirmed the idea that persons with skin cancers are predisposed to other skin cancers. There is also an indication that males with lip cancers have some predisposition to multiple skin cancers. There is no evidence that immunity to the formation of a second primary cancer is elicited by the presence of a skin cancer. In rabbits, Greene and Strauss[48] reported that 55 cases of multiple primary tumors (including cases with cutaneous carcinoma) were found in a colony of rabbits over a 17-year period. Analysis of the incidence showed that while one neoplastic focus

neither predisposed toward nor against the formation of another, the presence of one focus did exert an inhibiting effect on the progress of the others in its development to cancer.

METASTATIC CUTANEOUS MALIGNANCY.* Gates's[44] article on malignancy metastatic to the skin is still one of the classics in this field. Further study has not indicated a particularly increased incidence of cutaneous metastases of malignant disease. Barksdale, Walters and Kern[9] have summarized most of the features of metastatic carcinoma as well as the cutaneous manifestations of the lymphoblastomas.

METASTATIC CUTANEOUS MALIGNANCY

I. Metastases reach skin by:
   1. Direct spread from underlying tumors, such as direct extension through abdominal wall from carcinoma of gallbladder.
   2. Direct spread through lymphatics, for example, carcinoma *en cuirasse*.
   3. Dissemination through lymphatics.
   4. Dissemination through blood stream.

II. Sites of origin for cutaneous metastases:

Breast	50%
Stomach	15 to 31%
Lung	12%
Uterus	9%
Kidney	9%

III. Other features:
   1. Cutaneous metastases relatively rare, with incidence varying from 1 to 2.7%.
   2. Metastases generally confined to region of primary growth, for example, carcinoma of pelvic organs when metastasizing to skin usually does so to skin of groin, perianal and pelvic regions.
   3. Some tumors have predilection for scalp, namely, 33% of carcinomas of breast and 20% of others.
   4. Cutaneous metastasis has no characteristic clinical appearance. Except in cases of carcinoma *en cuirasse* usually appear as discrete, asymptomatic nodules.
   5. Histopathology generally approximates that of the primary growth.
   6. Cutaneous metastases are generally indicative of progression and early fatal termination.

The routes of involvement have been further elaborated by Mohs and Lathrop[78]. In some cases, "silent" extensions, unexpected by clinical visualizations and palpation, were due to a peculiar affinity of the cancer for some specific tissue structure which it would follow selectively for unexpectedly great distances. Some structures for which certain cancers showed particular affinity were: (1) dermis; (2) fascial planes; (3) periosteum; (4) perichondrium; (5) embryological fusion planes; (6) nerve sheaths; (7) lymphatic vessels, and (8) blood vessels. In other cases no specific affinities were observed but nevertheless irregular outgrowths were present, apparently as a result of the countless local variations in the mechanical and nutritive conditions for the spread of cancer. Gonzaga[45] presents evidence to support the belief that lymphatic dissemination is responsible for metastases to the skin (22 cases). In some cases the primary cancer had been cured and cutaneous lesions were the first sign that generalization had occurred. The lesions were at times simple extension of Paget's disease, sometimes secondary to carcinoma which had direct access to the

*Discussion of cutaneous tumors metastasizing to the viscera is omitted. It may be pertinent, in passing, to note the increasing number of studies reporting basal cell epitheliomas metastasizing to lymph nodes and viscera[4,61,99].

major circulation as in one case of cardiac and one case of pulmonary cancer. There were other cases with direct and indirect lymphatic connection between the primary tumor and site of metastatic lesion. Metastases from gastric carcinoma usually appear in the abdominal wall, presumably by spreading along the lymphatics of the round ligament of the liver. This explanation presupposes the existence of hepatic metastases, which are common in gastric cancer. Histologic evidence of hematogenous dissemination was lacking (no invasion of vessels or thromboses) but there were signs of propagation through the interstices of the dermis, lymphatic sheaths of vessels and nerves, and along hair follicles and sweat glands. Long periods of latency sometimes precede the appearance of the metastases, 12 years in one case of breast cancer. The histologic appearance of the primary and secondary lesions is identical. In other cases, secondaries may precede discovery of primary lesions.

Since 1946 a variety of localizations and types of cutaneous metastases have been described: Inflammatory diffuse cutaneous metastatic carcinoma from epidermal carcinoma of the vulva (Cianfrani and Smith, Obstet. & Gyn., 8, 500, 1956), adenocarcinoma of the lip secondary to adenocarcinoma of the stomach[29]; cancer of the pancreas[33]; metastatic hypernephroma in nasal septum[1]. Likewise, Burns, Edwards, Pessel and Cowlbeck[22] reported an example of metastasis to the nasopharynx with epistaxis the presenting symptom. We have seen tissue from 3 cases of hypernephroma with cutaneous metastases recently. This kidney tumor has a singular capacity to give rise to solitary (cutaneous) metastases often many years after removal of the primary tumor. McDonald and his coworkers[72] reported that cutaneous metatases secondary to carcinoma of the urinary bladder are rare. They found 10 cases in the literature between 1922 and 1948. Examination of the records of the Presbyterian Hospital of Chicago from January 1, 1903, to January 1, 1949, revealed that of 453,891 patients admitted to the hospital, 11,265 had the diagnosis of cancer. Thirty-three (0.29% of cancer patients) had cutaneous metastases. The primary lesions were in the breast in 19, in the rectum in 5, in the stomach in 2, one each in the sigmoid colon, the uterine cervix, an ovary, a parotid gland, and the thyroid gland. Of 1,114 patients with primary carcinoma of the bladder, two (0.18%) had cutaneous metastases. (See also Wormer *et al.*[107a] and Bischoff and Fishkin[17a].) Scott, Head and Mack[97] in their study of cutaneous metastases from tumors of the bladder, urethra and penis found literary reference to cutaneous metastases from the adrenal glands, the kidneys, the ovaries, breasts, pancreas, parotid gland, the tonsils and the ureters. They found 16 cases of bladder cancer with cutaneous metastases in the literature and added 4 cases of their own (all men). Barenghi[8] reported an example of prostatic carcinoma with cutaneous and osseous metastasis.

By far the most common origin for cutaneous metastases is carcinoma of the breast. In our previous report it was noted that carcinoma of this organ was followed by as many secondary cutaneous tumors as all other types together. Carcinoma of the breast can produce cutaneous metastases which show a highly diversified clinical picture[7,42,51,63,82]. The commonest type of metastatic carcinoma from the breast is inflammatory carcinoma. Lee and Tannenbaum[64] reported 28 cases. This type of metastatic cutaneous lesion occurs in 1.3% of all mammary cancers. Other names for cutaneous metastases from carcinoma of the breast are: mas-

titis carcinomatosa; acute breast cancer; erysipelas carcinomatosa. Less characteristic metastatic cancer of the breast is carcinoma telangiectaticum (Weber[106]). In his case, the skin over the breast contained numerous pink papules or pseudovesicles. Nix[84] described a similar case, skin with purple papules resembling hemolymphangioma. Nanta and Salvador[80] have described pink, red, purple, and black papules. They called this cutaneous angioepitheliomatosis. In the corium there were dilated endothelium-lined spaces containing malignant tumor cells and varying amounts of blood cells. Color depends on the amount of blood in the affected capillaries. In the third type, carcinoma *en cuirasse*, there are sheets of cancer cells throughout the corium and the chest usually becomes gradually thickened and more firm. Occasionally, this type is not diffuse and a nodular variety can result. Rarely, 2 or more of these 3 forms may co-exist. Leavell and Tillotson[63] reported a case in a woman of 57 with all 3 types of cutaneous metastases: (1) in the opposite breast skin 2 years after radical mastectomy there were small pink papules with malignant cells in endothelium-lined spaces (carcinoma telangiectaticum); (2) on the left breast (right mastectomy) at the same time there was redness and slight induration of the skin and pathologically there were small groups of malignant tumor cells with adjacent perivascular inflammatory infiltrate in the upper part of the corium (inflammatory carcinoma); (3) appeared in the skin of the epigastric region 6 months after the first 2 and was composed, clinically, of ill-defined thickenings of the skin. Pathologically there were small groups of malignant tumor cells throughout the fibrosed corium (nodular carcinoma).

Fourteen (18.9%) of the 74 cases seen at Mayo Clinic between 1933 and 1945 were erroneously diagnosed as inflammatory disease before the carcinoma was discovered. Siegel[98] presented a case of primary inflammatory cancer of the breast in which the first manifestation was a solitary red area on the side of the neck with subsequent involvement of the breast on the same side. This process resembled and was treated as erysipelas.

Stewart and Treves[103] in 1948 reported an interesting lesion in postmastectomy lymphedema which they interpreted as lymphangiosarcoma. A similar case was reported in 1950 by Ferraro[38]. This has become a rather well known syndrome, and in 1952 Jessner, Zak and Rein[56] summarized the subject in the dermatologic literature. All reported cases occurred in women 46 to 68 years old. Various degrees of postoperative edema of the arm are an early and eventually a permanent sign. The time interval between the operation and the appearance of lymphangiosarcoma varied in their cases from 6 to 24 years. As 70% of patients undergoing radical mastectomy demonstrate swelling of the arm, knowledge of the disorder assumes practical importance. Daland[32] in his review of the subject of postmastectomy elephantiasis stressed certain points to be observed in order to avoid this complication. Since these tumors are not radiosensitive, early and radical amputation may prove a lifesaving procedure. The pathologist, likewise, should become familiar with this syndrome and consider it whenever a Kaposi's sarcoma-like picture is encountered in lymphedema, clinically and microscopically, following mastectomy. Not having been able to perform microscopic examinations of the amputated arm, Jessner, Zak and Rein's findings are not as complete as the excellent descriptions in the article by Stewart and Treves which are based on exami-

nation of amputated arms in addition to skin biopsies. Thus, formation of lymph follicles and perivascular arrangement of tumor around deep veins, also seen by Ferraro[38] was not observed by these authors. In their case, there was a tendency of tumor cells to deposit reticulin. This feature was not previously mentioned. Since many of the lesions appear dark red clinically, the authors consider that they must consist of a mixture of lymphatics and blood vessels rather than being purely lymphangioblastic, an observation corroborated by microscopic examination, even with due allowance for hemorrhage caused by biopsy trauma. Jessner and his coworkers concur with the first observers that radiation treatment is not effective for this condition and that early, radical, that is, interscapulothoracic amputation, is indicated as soon as a definite diagnosis is made. The absence of tumors of this nature in elephantiasis not related to cancerous disease, for example, filariasis, has led Stewart and Treves[103] to postulate the presence of a carcinogen which, under favorable conditions like chronic lymphedema, will produce an angioblastic tumor. It is up to experimental workers to study this thesis. In this connection it should be stressed that the lesions of Kaposi's sarcoma may be preceded by chronic edema. Another possible explanation might be found in the startling observation of Toolan and Kidd[104] who found that mammary carcinoma cells which had sojourned in immune mice produced sarcoma-like pictures, including the property of reticulin formation. The possible connection between this observation and the Stewart-Treves syndrome is obvious but remains to be proved.

EXTRAMAMMARY PAGET'S DISEASE. While not, strictly speaking, a cutaneous metastatic lesion, it is appropriate to discuss extramammary Paget's disease here. In spite of the interest recently expressed in this form of Paget's disease, the fundamental problem as to its nature and actual incidence hold the fore. As previously defined, extramammary Paget's disease refers to those cases in which the lesion occurs apart from the breast and its covering skin, and is from the standpoint of histology entirely similar to the classic lesion in the breast (that is, epidermal changes, essentially identical with those observed in Paget's disease of the nipple and areola), and in addition, carcinoma of the underlying sweat glands. The recent literature has not fully elucidated the actual nature of this process. Lennox and Pearce[65] have found mucus in the cells of extramammary Paget's disease but none in the cells of mammary Paget's disease. Although there is lessened tendency to doubt the existence of extramammary Paget's disease, there is still much difference of opinion as to its actual incidence. For example, Pinkus[88] controverts the statement by Greeley and Curtin[46] that their case was the thirty-eighth published example rather than the twenty-eighth. Pinkus furthermore logically points out that "It is likely that the exact number of proved cases of extramammary Paget's disease will never be known, particularly since such cases are diagnosed as a routine matter by dermatologists and pathologists every year."

One fact about this disease is clear. More and more frequently are examples of it reported in a variety of journals. A cursory examination of some of the recent literature contains references to the following cases: perianal region[39,47,81,111]; vulva[2,24,34,55,76,77,90,101]; male genitalia[46]. Greeley and Curtin[46] make the pertinent statement that Paget's disease might well be called Paget's dermatosis, of which involvement of the nipple is the most frequent example. Extramammary Paget's disease has been reported

to occur where apocrine sweat glands are located (male genitalia; female genitalia; axillae and perianal skin)[89].

CUTANEOUS LESIONS AND INTERNAL CANCER.* In 1925 Rothman[94] classified the cutaneous disturbances accompanying malignant tumors of internal organs as follows: (1) pruritus and a prurigo-like syndrome with hyperpigmentation; (2) toxic bullous eruptions; (3) metastatic cutaneous lesions and inflammatory lesions preceding metastases; (4) acanthosis nigricans and similar proliferative changes. Later, Becker, Kahn and Rothman[10] surveyed the literature and reported two cases. They suggested that carcinoma cells might be destroyed in the skin by cutaneous defense mechanisms and that clinical manifestations of the defense reaction might be either necrosis or inflammation. Forman[10] too has discussed this problem. According to Barksdale, Walters and Kern[9] the cutaneous manifestations of lymphoblastomas are:

A. Specific or true neoplastic infiltrations.
B. Nonspecific or toxic reactions:
   1. Pruritus.
   2. Eczematoid, psoriasiform, urticarial, erythema multiforme-like, bullous and pemphigoid lesions.
   3. Purpuric and hemorrhagic lesions.
   4. Herpes zoster and herpes simplex.
   5. Exfoliative dermatitis.
   6. Stomatitis.
   7. Pigmentation.
   8. Elephantiasis.
   9. Alopecia.

Costello and his group[28] have described the (specific and nonspecific) cutaneous manifestations of myelogenous leukemia. Bluefarb and his associate[20] of Chicago, too, have been most active in the field of correlation of the nonspecific manifestation of the leukemia-lymphoma group and external cancer. They have listed what they call the "Eleven P's,": pallor; pruritus including urticaria; prurigo-like papules; pyoderma; pigmentations, including acanthosis nigricans; pemphigoid or bullous lesions; pityriasis rubra or exfoliative dermatitis; posterior ganglionitis or herpes zoster; purpura, petechiae and other vascular phenomena; poikilodermatomyositis; phlebitis. The incidence of nonspecific cutaneous manifestations will vary with each disease. Cutaneous changes due to internal malignant tumors appear to be rare but may occur as a consequence of any type of malignant tumor in any location, mostly as late manifestations and usually after the occurrence of considerable necrosis of the tumor cells. Ziegler[110] estimated that in 20 cases of Hodgkin's disease 25% presented cutaneous manifestations and the lesions appeared in 5 to 12% of the cases before any other sign of Hodgkin's disease. Other writers have reported a frequency of 15 to 53%, the higher incidence being reported by dermatologists who would be more observant of skin manifestations. The average incidence of cutaneous manifestations in Hodgkin's disease, it would appear, is from 25 to 35%, and in about 10% of cases cutaneous manifestations were the initial symptom[18].

Other isolated examples of dermatologic sequelae include Murrell and Pepple's report[79] on 2 cases: (a) malignant metastases in the skin from the testicle; (b) dermatological condition (comedo-like lesions on chest, above waist and extending onto the forearms,

*In functioning carcinoid tumors the cutaneous vascular lesions are the most characteristic and consistently recognized of all the clinical features. These lesions are usually manifested by some form of paroxysmal or persistent erythematous flushing of the skin, predominantly on the face and neck, but variable in extent and location[70a,92a].

as well as follicular comedo-like lesions involving the butterfly region and the regions just anterior to the auditory canals. The back and chest had acne-like inflammatory lesions). Murrell and Pepple believe there was a direct relationship between the lesions and the testicular tumor, largely because of improvement with Roentgen-ray and surgical therapy (testicular region).

Ronchese[93] reported a case of alopecia of the scalp resembling alopecia cicatrisata, from metastases of an adenocarcinoma of the breast. Metastatic alopecia deserves mention among the noncicatricial symptomatic alopecias. Its recognition may help in the early diagnosis of internal malignancy.

CARCINOMA AND DERMATOMYOSITIS. Although others (Zarafonetis[109a], for example) have noted the association of cancer and dermatomyositis, Dowling[35] has given a good summary of this association. Over a period of 20 years he found a considerable number of case histories and necropsies had been reported which pointed to the somewhat frequent association of dermatomyositis with visceral malignant disease. Schuermann[96] reviewed 336 published cases of dermatomyositis and found among them 31 with associated malignant growth. Subjecting these figures to statistical analysis Schuermann discovered that the incidence of malignancy in dermatomyositis is 5 times that in the normal population. He found no record of malignancy in his own practice and in the current literature over a period of 20 years in 600 cases of progressive scleroderma. (But see scleroderma associated with cancer of the lung [Jonsson and Houser[56a]] and terminal bronchilar [alveolar-cell] carcinoma in scleroderma [Zatuchni, Campbell and Zarafonetis[109b]].) Dowling observed that in 25 published cases the histories were very similar. In nearly all, the symptoms were acute with a good deal of edema and severe muscular weakness, but in a few the skin changes were those of chronic dermatomyositis. In all, malignancy appeared likely to have preceded the onset of dermatomyositis. In 4 cases[17, 21,36] treatment of the malignancy by operation or by radiotherapy was said to have been followed by improvement in or disappearance of the cutaneous and muscular symptoms. The symptoms followed the characteristic muscular and cutaneous pattern and they evidently had not differed from acute or chronic dermatomyositis unassociated with malignancy. Three of the comparatively recent series of 20 cases at St. Thomas's Hospital had associated malignant disease, one ovarian and two pulmonary. In one, an ovarian carcinoma preceded the dermatomyositis by 15 months. In the second, a small lung shadow was discovered at the time of admission to the hospital, and this increased in size during the course of the illness. This patient also had Raynaud's symptoms. He died of dermatomyositis in just under 2 years after the onset of the disease, and at necropsy he was found to have a bronchial carcinoma. The third patient, a man of 64, presented himself in the outpatient department with acute livid telangiectatic erythema together with gross edema of the face and arms. He had sailed a dinghy the previous day and had been perfectly fit up to the day of admission. The diagnosis of dermatomyositis was made rather than acute lupus erythematosus because of the edema. Within a few days the patient was completely prostrate and he died within 6 weeks of the day of onset of the illness. A carcinoma the size of a small pea at the periphery of the lung with secondary deposits in regional glands was discovered at necropsy. The muscles were completely disintegrated.

The principal facts are assembled in

a table which appears strongly to support a relationship between malignancy and dermatomyositis when they are associated. It is also shown that the order of events has been malignancy followed by dermatomyositis and that when death occurred, dermatomyositis and not malignancy was the cause in almost every case. More recently Christianson, Brunsting and Perry (A.M.A. Arch. Dermat., **74**, 581, 1956) of the Mayo Clinic made a survey of the records of 270 patients with dermatomyositis. They found associated malignant diseases in 6.7% of the cases.

The beautiful exhibit by Curth[31] entitled, "Dermatoses and Malignant Internal Tumors," deals with non-neoplastic cutaneous lesions *associated* with malignant internal tumors. She indicated that recognition of these combinations may help cancer research by providing material for an understanding of the principle by which a tumor has produced cutaneous changes. Also, it may guide in a definite direction the search for a tumor in cases in which the dermatosis precedes the manifestation of internal cancer. The following outline is based on her work.

	Clinical Picture	*Tumor Type*
Pruritus	Patients complaining of severe generalized itching subsequently show signs of internal neoplasm. Pruritus may lead to a prurigo-like syndrome with discrete or diffuse hyperpigmentation.	Cancer of gastrointestinal tract especially stomach, or of breast or carcinoma of ovary with metastasis; abdominal and thoracic tumors; lymphosarcoma; Hodgkin's disease; and leukemia.
Urticaria	Persistent, more or less generalized wheals associated with itching in patients suffering from malignant neoplasm.	Cancer of rectum, hydatidiform mole, Hodgkin's disease.
Acquired Ichthyosis (Ichthyosiform Atrophy of Ronchese)	A patient without personal or familial history of ichthyosis shows generalized dry and cracking skin, hyperkeratotic palms and soles, and alopecia. At the same time Hodgkin's disease or a lymphosarcoma becomes evident.	Hodgkin's disease or lymphosarcoma.
Syndrome of Generalized Intestinal Polyposis and Melanin Spots of Oral Mucosa, Lips, and Digits. (Peutz, 1921)	Numerous pigmented spots, varying from light brown to deep blue-black on lips (on vermilion border and mucous membrane side and more numerous on lower than on upper lip), and buccal mucosa (usually in large blotches). Some patients show, in addition, small pigmented spots on face (about mouth), fingers, and toes. Anemia, melena, and periodic attacks of abdominal pain, frequently due to intussusception, are common. Several members of a family may be involved (see Beerman and Colburn).	Polyposis distributed throughout the gastrointestinal tract, but the small intestine, particularly the jejunum, is predominantly involved. Jeghers, in a personal communication to Curth, points out that he "strongly suspects that malignancy will become a great hazard if patients live to be 40 or more"; in 2 of 15 cases known to Jeghers, transition from polyp to malignant tumor, however, has already been observed.
A Syndrome of Multiple Cutaneous and Subcutaneous Lesions Occurring Simultaneously with Hereditary Polyposis and Osteomatosis. (Gardner, Plank, and Richards)	Several members of a family in Utah show "soft tumors," intestinal polyps, and osteomas; one child has minor bone changes but no intestinal polyps.	Multiple intestinal polyps, especially of large intestine. Eight of thirteen deceased members of family died of carcinoma of colon or rectum. They presumably had multiple polyposis and were known to have had subcutaneous tumors or cysts.

	Clinical Picture	*Tumor Type*
Pachydermoperiostosis	Thickening of skin, accentuation of existing and creation of new folds; the forehead especially shows deep horizontal lines and shiny skin. The lids, particularly the upper ones, are thickened; so are the ears and lips. Macroglossia. The scalp may be involved (cutis verticis gyrata). The extremities, especially the elbows, knees, and hands, are enlarged. The fingers are clubbed. The palms are rough, and thenar and hypothenar eminences are enlarged. Movements of muscles are painful. At this time pulmonary cancer has become evident.	Bronchogenic carcinoma.
* Malignant Acanthosis Nigricans	Hyperpigmented verrucous confluent lesions of body folds, nipples, umbilicus, perianal areas, and others, with occasional involvement of mucous membranes and occasional keratoderma of palms and soles in patients who have shown, are beginning to show, or will show signs of adenocarcinoma. Sex: 50% males and 50% females. Age: The disease is rare in children; at onset of dermatosis most patients are adults, and the majority of them are over 40 years old. Another form, not associated with tumor, is called "benign."	Highly malignant adenocarcinoma of stomach, liver (?), pancreas, esophagus, gallbladder, intestine, uterus, ovary, mammary gland, and lung. In some cases primary site of tumor could not be determined with certainty but lymph nodes showed adenocarcinoma.
† Dermatomyositis	Characteristic changes of skin (of face, scalp, neck, and upper and lower extremities), muscles (especially those of shoulder girdle, arms, and neck), and inner organs (particularly the heart) in patients in whom a tumor is present or supervenes shortly.	*In women:* Frequent: adenocarcinomas of ovary (often bilateral), sometimes tumors of granulosa cell origin: adenocarcinoma of breast (sometimes bilateral). Less frequent: Squamous cell carcinoma of cervix or vagina; osseous sarcoma; multiple myeloma, retroperitoneal sarcoma, and tumors of parotid gland. *In men:* Cancer of stomach, esophagus, gallbladder, kidney, and lung; also leukemia, lymphosarcoma, and Hodgkin's disease. *Note:* The relatively high incidence of bilateral ovarian and mammary cancers is noteworthy: Incidence in Cases of Dermatomyositis.—In 17.7% (Curtis, Blaylock, and Harrell, Jr.) 12.9% (Schuermann) (See also Forman)

* See also Beerman and Colburn[12]; Kierland[59]; and Curth (1952).[30]

† Jonsson and Houser have reported a case of scleroderma (progressive systemic sclerosis) associated with cancer of the lung (Jonsson, S. M., and Houser, J. M.[56a]). Also Storkan, Rea and Becker[103a] observed poikilodermatomyositis associated with adenocarcinoma (bronchogenic?).

	Clinical Picture	*Tumor Type*
Erythema Multiforme (Toxic Erythema) *In patients who received radiation therapy for tumor.*	Generalized erythematous, papular, papulovesicular, bullous, scarlatiniform, or exfoliative eruptions in patients who received deep Roentgen-ray or radium therapy for malignant tumors or postoperatively. The eruption is often associated with fever and other constitutional signs; it subsides after several days. (Rothman observed a dermatitis-herpetiformis-like eruption following Roentgen treatment of round cell sarcoma of thyroid.)	Cancer of tongue, stomach, uterus, and breast; bronchogenic carcinoma; mediastinal lymphoblastoma; retroperitoneal lymphosarcoma, and myosarcomatosis.
Erythema Multiforme (Toxic Erythema) *In patients who did not receive radiation therapy for tumor.*	Generalized erythematous (sometimes simulating eruption of lupus erythematosus), papular, papulovesicular, bullous, or polymorphic lesions in patients with malignant tumors.	Cancer of stomach, metastatic adenocarcinoma originating in adrenals or lung, retroperitoneal sarcoma(?).
Erythema Gyratum Repens	On trunk, neck, and extremities irregular, wavy bands with peculiar gyrate or serpiginous outline, which is constantly changing. The lesion shows marginal or collarette type of desquamation. At the time of development of the dermatosis, a primary tumor or metastasis is noted.	Adenocarcinoma of breast with metastases and anaplastic oat cell carcinoma of lung. (See Gammel)
Herpes Zoster	Characteristic unilateral eruption corresponding to course of spinal or cranial nerves. In patients suffering from neoplastic disease, generalized herpes zoster. At the time of the development of the dermatosis the neoplasm has already been apparent. The majority of patients, but not all, had received radiation therapy for tumor prior to outbreak of dermatosis.	Lymphosarcoma, Hodgkin's disease, lymphatic leukemia; less often myeloid and monocytic leukemia. Tumors of women: Cancer of breast or uterus, and carcinoma or sarcoma of ovaries. Tumors of men: Gastric cancer and seminoma. Among the neoplasms those with metastases prevail.

Incidence of Herpes Zoster in

Hodgkin's disease	4.5% (Craver and Haagensen)
Hodgkin's disease	0.06–13.4% (Various authors)
Lymphosarcoma	7.0% (Craver and Haagensen)
Lymphatic leukemia	0.9% (Craver and Haagensen)
Mammary cancer in general	4.0% (Pendergrass and Kirsh)
Mammary cancer with metastasis	5.0% (Pendergrass and Kirsh)
Mammary cancer without metastasis	3.0% (Pendergrass and Kirsh)

Note: In the general population herpes zoster constitutes 1% to 2% of all dermatoses.

Dermatitis Herpetiformis	Grouped papulovesicular lesions on erythematous base on trunk and extremities with occasional involvement of oral mucous membranes in patients with malignant tumor.	Necrosis is present in some but absent in other tumors. Papillary cancer of ovary with central necrosis; carcinoma or sarcoma of thyroid; adenocarcinoma of uterus; cancer of vulva, cervix, pancreas, stomach; choriocarcinoma; deciduoma; Hodgkin's disease.

Curth concludes her discussion as follows: "Intestinal polyposis figures in various syndromes. Polyposis, particularly of the small intestine, is associated with pigmentation of the oral mucosa, lips and digits, while polyposis, particularly of the large intestine, is associated with multiple characteristic cutaneous and osseous changes. In both instances transition from polyp to adenocarcinoma has been observed. Lung tumors are associated with pachydermoperiostosis. Highly malignant adenocarcinomas of various internal organs are found in association with 'malignant' acanthosis nigricans. Tumors of the reticuloendothelial system and Hodgkin's disease occur with acquired ichthyosis.

"Present in the two observations of erythema gyratum repens were mammary adenocarcinoma and anaplastic oat cell carcinoma.

"Not limited to special types of locations are the tumors occurring in combination with other dermatoses. However, dermatomyositis shows a relatively high incidence of accompanying bilateral ovarian and mammary tumors—not found in association with other dermatoses. The possibility that it is the necrosis of a tumor which causes cutaneous eruptions finds some support in observations such as the one which showed that only a necrotic tumor, and not the recurrent neoplasm without necrosis, was accompanied by dermatitis herpetiformis. Tumors treated with deep irradiation—shortly prior to the cutaneous outbreak—are accompanied by transitory erythema multiforme-like eruptions. Persistent erythema multiforme occurs with adenocarcinoma and sarcoma.

"Not yet proved is the relationship between tumors and scleroderma, lupus erythematosus, or unilateral nevus.

"Associated with the various malignant internal tumors are inflammatory, pigmentary, proliferative, atrophic, vascular, or nevoid cutaneous changes, sometimes in combination. In some syndromes the cutaneous process is regularly accompanied by similar disturbances in other systems, such as muscles, bones, etc.

"Various principles seem to play a role in the relationship between the tumor and the dermatosis. Genetic relationship explains the associations of intestinal polyposis and cutaneous or osseous changes, or both. A genetic predisposition to tumor and dermatosis may be underlying 'malignant' acanthosis nigricans. In addition, the cancer activates acanthosis nigricans. The tumor which leads to pachydermoperiostosis is complicated by anoxemia of peripheral tissues. Substances of irradiated and non-irradiated, as well as of necrotic or non-necrotic, tumors may cause toxic or allergic cutaneous reactions. Alteration of liver function due to neoplasm or metastases may lead to changed vitamin A and B metabolism and a disturbed estrogen-androgen balance. Hormonal imbalance may play a role in many tumors. Some tumors may even produce nonphysiological steroids. By mechanical means or toxic effects the (irradiated) tumors or leukemias may create ideal conditions in the afferent portion of the reflex arc for the activation of the herpes zoster virus.

"While disappearance of the dermatosis after removal of the tumor and reappearance of the dermatosis with recurrence of the tumor point to some causal connection between tumor and dermatosis, it would be wrong to assume the tumor to be the sole cause of the cutaneous eruption in every such instance. The catabolic substances of neoplasm may serve as the trigger mechanism for skin predisposed to various pathologic processes by genetic, allergic, or other factors."

CARCINOMA OF THE SKIN FOLLOWING

OR SECONDARY TO CUTANEOUS DISEASE. A variety of cutaneous disorders have been known to be followed by the development of cutaneous cancer. Nilssen[83] in 194[illegible] observed 11 such cases. These included examples of carcinoma developing in lupus erythematosus, 4 of lupus erythematosus cancer and one instance of carcinoma in Boeck's sarcoid.

Halpern[49] states that epithelioma has been known to occur in chronic cutaneous diseases: psoriasis; eczema; hypertrophic lichen planus and blastomycosis; scar from burns; trauma; syphilis; tuberculosis; lupus vulgaris and lupus erythematosus and scars. Halpern reported a case of epidermolysis bullosa in which bilateral squamous cell epithelioma of the legs developed in a 53-year-old white man. Rasponi[91] observed 2 similar cases. Michailowski[75] as well as Touraine and Lambergeon[105] have reported cases of the development of carcinoma in patients with cheilitis glandularis. Parkin[86] observed an example of nevus sebaceus on which a prickle cell carcinoma developed. Maier[70] presented a case of metastatic sweat gland carcinoma superimposed on nevus syringo-adenoma papilliferus. Hodgson's[52] patient with pruritus ani developed carcinoma of the perineum after application twice a day for 2 years of tar preparation (liquor picis carbonis). Tar applications for medicinal purposes rarely produce this result. However, industrial exposure to tar not infrequently results in cancer and recently Lenson[66] reported the case of a patient with multiple cutaneous carcinoma after creosote exposure. Lupus vulgaris has been followed by carcinoma[50,54]. Auger[6] reported a case of reticulosarcoma occurring in a tattoo.

CARCINOMA ARISING IN THE SCARS OF THERMAL BURNS. Lawrence[62] analyzed the histories of 11 patients treated for thermal scar cancers at the Indiana University Medical Center and of 82 cases reported in the literature. Only those cases were selected for study in which the age of the patient at the time of the burn and the recognition of the cancer were known. In this series there were 80 cases of epidermoid carcinoma as verified by microscopic study. A striking histological feature in this type of cancer was the abruptness with which the marginal hypertrophied epithelium changed to frank neoplastic tissue. Abnormal epithelium was present in all of the cases in the bed of the ulcer. The study of the time element demonstrated that, when the mean age at the time of burn increases, the length of the mean latent period decreases. The mean age at the time of diagnosis of cancer in the entire series was 47.2 years, while the mean ages at the time of the diagnosis of epidermoid carcinoma in the skin of unburned patients reported from the Massachusetts and Huntington Hospitals were 67.2 and 68.2 years, respectively. This study failed to reveal any specific environmental hazard that appeared to influence the inception of the malignant process. The origin of the neoplasm, Lawrence felt, was probably due to the effect of surface phenomena rather than to agents enveloped in the scar at the time of the burn. The length of the induction period was inversely proportional to the age of the patient at the time of the burn. Grafting of the wound at the time of the burn, according to Lawrence was the best prophylactic measure.

RADIODERMATITIS. It has been the general belief that the carcinoma developing as a consequence of radiodermatitis is of the prickle cell variety. The Andersons[5] have demonstrated that such carcinomas are not invariably of the prickle cell type and report a number of instances in which the ensuing

carcinomas were basal cell in character.

LUPUS ERYTHEMATOSUS. Holtzman[53] as well as Ryan[95] have observed cases of chronic discoid lupus erythematosus complicated by prickle cell epithelioma. This phenomenon is undoubtedly not related, as some believe, to Roentgen-ray therapy. Ryan stated that there are more than 100 cases in the literature in which none of the physical agents (Roentgen ray, radium or carbon dioxide snow) was used.

PSORIASIS. Levin[67] records a case of universal psoriasis with tumor-like formations (parakeratosis scutularis; parakeratosis ostracea). Arsenic was eliminated as the cause. Levin presented the patient again in 1939[68]. He noted that since 1937 the nodule had increased in size and had become ulcerated. In 1934 biopsy examination of one lesion showed evidence of squamous cell epithelioma. Keil and Trosow[57] reported a similar case and infer that there is a definite syndrome in which long-lasting psoriatic erythroderma is accompanied subsequently with the appearance of nonulcerated wart-like growths on various parts of the body, especially the legs. These growths are probably forerunners of epitheliomatous changes of various types. Others, too, have reported epitheliomas developing in psoriatic patches[41,108]. Arsenical therapy apparently was not a factor in these cases.

GRANULOMA INGUINALE. The relationship of granuloma inguinale to cancer, in contrast to that of lymphogranuloma venereum, has not been defined. That is, does granuloma inguinale imitate cancer, and *vice versa;* does cancer develop on lesions of granuloma inguinale; or do cancer and granuloma inguinale occur independently in the same patient? Although some authors deny that cancer may occur as a complication of granuloma inguinale, the experience of others, as well as that of Beerman and Sonck[14] with several patients who had granuloma inguinale and in whom cancer was discovered in the granuloma inguinale lesion, led them to re-examine this problem. Beerman and Sonck believe that in unquestionable granuloma inguinale, the epithelial changes microscopically may range from normal epidermis to such a degree of hyperplasia that epithelioma may be ruled out with difficulty, and they demonstrated that there are cases in which epithelioma co-exists with, or is mistaken for, granuloma inguinale clinically and histologically. Granuloma inguinale has been confused with carcinoma since the end of the nineteenth century when Conyers and Daniels[27] and Galloway[43] felt that granuloma inguinale was a new growth or tumor. Since then numerous authors have reported cases of this disease diagnosed as, or simulating, cancer. In many of these cases, pseudoepitheliomatous changes were prominent features microscopically but differential diagnosis was usually possible. Another group of investigators reported instances of cancer diagnosed as granuloma inguinale. Although Donovan bodies were said to be present in 2 of Kern's[58] 3 patients whose lesions resembled granuloma inguinale clinically, the histopathologic findings and clinical course left no doubt as to the cancerous nature of the lesions. There are a number of reported examples of the co-existence of cancer and granuloma inguinale[23,25,26,73]. Clearkin[25a] observed not only squamous cell carcinoma but the basal cell type as well.

MULTIPLE ARSENICAL CANCERS OF THE SKIN AND INTERNAL ORGANS. Sommers and McManus[100] reviewed 27 cases of arsenical cancer in 19 men and 8 women. Twelve had been treated for

psoriasis with Fowler's (potassium arsenite) solution; one had received injections of arsenicals because of syphilis; two had had occupational exposure to arsenical sprays; and in four others occupational exposure seemed possible. Seven had been treated with arsenic for swollen lymph nodes, burns, dermatitis, or chorea. In three, the form of exposure was unknown. The arsenical origin was recognized clinically in all except one of the cases by the characteristic multiple keratoses of palms and soles. In addition to the large number and extent of multiple skin cancers, 4 of the 6 patients who came to necropsy had additional internal cancers, 3 at multiple sites. These visceral lesions were in the bladder, prostate, esophagus, colon, kidney, and chest wall. In 5 other patients who died, death was ascribed to cancer of the tonsil, esophagus, breast, pancreas, and lung. One patient with multiple skin cancers and lung cancer is living. Some skin lesions apparently developed from the epidermis, sweat, or sebaceous glands, and possibly hair follicles. Gradations of epidermal atrophy, hyperplasia, precancerous changes, carcinoma *in situ* (Bowen's disease), and invasive cancers were observed. The visceral cancers suggest that a second predisposed tissue is the squamous epithelium of the respiratory tract. The third region of predilection is the urogenital epithelium of the kidney, ureter, and urinary bladder. Heredity, chronic irritation, local sensitivity and endocrine abnormalities may favor arsenical carcinogenesis. Present knowledge of the biochemical effects of arsenic suggest that it influences hydrogen transport, nucleoprotein metabolism, and phosphorylation. It acts mainly on the nucleus and interferes with mitosis. The consequences are visible cytologically as disturbed epithelial growth and delayed maturation, particularly in epidermal nuclei. Mechanical stimuli, Roentgen rays, and hormonal imbalances may have additional carcinogenic effects.

CARCINOMA AND MYCOSIS FUNGOIDES. The association of carcinoma and lymphoblastoma is not common. This is especially the case in the simultaneous occurrence of carcinoma and mycosis fungoides. This view was confirmed by Beerman and Thomas[15] who found that only rarely is mycosis fungoides simultaneously associated with other diseases. They reported a case, a Negress, who had during a period of more than 20 years a series of seven neoplastic and ectodermal abnormalities, as follows: ovarian cyst, fetal adenoma of the thyroid, congenital ichthyosiform erythroderma, uterine tumor, carcinoma of the uterine cervix, mycosis fungoides, and adenocarcinoma of the rectum. Other examples of mycosis fungoides associated with various complications have been collected by Bluefarb, Ihrke and Steinberg[19]. In no instance was there evidence that carcinoma was the cause of the fatal termination. Bluefarb and his co-workers reported 2 cases in which there was a simultaneous occurrence of mycosis fungoides and carcinoma, one with carcinoma of the cervix and the other with multiple benign polyposis and adenocarcinoma of the descending colon.

RHINOPHYMA. Novy[85] presented the case of a 76-year-old man who had rhinophyma with carcinomatous degeneration. We, too, have seen one such case. Rees[92] has observed basal cell carcinoma in association with rhinophyma.

HERPES. Wyburn-Mason[109] discussed malignant transformation of herpetic skin lesions (zoster). He has seen numerous cases in which zoster lesions became transformed into basal or squamous epithelioma which developed

after complete healing of zoster lesions. With respect to malignant changes following herpes involving the breast, Wyburn-Mason has seen 15 cases after an interval varying from 3 months to 3½ years, during which evidence of nervous irritation was usually present in the involved area. Malignant change developed in the breast beneath. He observed one case of malignant change following herpetic lesions of the neck and larynx. Herpes zoster involving the mucosa may also undergo malignant change in the affected tissue.

CARCINOMA DEVELOPING IN SEBACEOUS CYSTS. Peden[87] found 14 cases of carcinoma in 832 sebaceous cysts removed, an incidence of 1.7%. This incidence does not justify considering sebaceous cyst as a precancerous lesion. However, in older patients who have had a sebaceous cyst of relatively long duration on the face or scalp, perhaps ulcerated, and in which a recent change in character, such as an increase in size has been observed, carcinoma should be suspected. The most common type of cancer found in sebaceous cysts is a well differentiated squamous cell carcinoma of low grade malignancy, and these usually have not metastasized when first seen. Basal cell carcinomas occur much less frequently. (*Cf.* Charache, H.: Am. Surgeon, **22**, 482, 1956.)

EPIDERMOLYSIS BULLOSA AND CARCINOMA OF THE SKIN. Wetteland and Hövding[107] reported a case of squamous cell epithelioma in a 26-year-old man with dystrophic epidermolysis bullosa. There were also squamous cell carcinomata of the pleurae, lungs, and paratracheal nodule but it was not possible to trace the primary origin of these tumors; it is assumed they arose from the cutaneous lesion. There are 5 other cases in the literature of the association of epidermolysis and cancer of the skin.

CARCINOMA DEVELOPING IN CHRONIC DRAINING CUTANEOUS SINUSES AND FISTULAS. In 1941 Bereston and Ney[16] reviewed the reports of all the cases in which metastasis had occurred from carcinoma developing in a chronic osteomyelitic sinus. They added reports of 2 cases of their own to the seven which they had accepted from the literature. Stewart *et al.*[102] reported a case with no visceral metastasis but only spread to the skin. There are 4 cases in which proved metastatic lesions definitely occurred in the viscera and only one in which cutaneous spread was noted. Bereston and Ney concluded that the rarity of metastasis may be explained by the low-grade of malignancy and by the possibility that some of the reported cases may have been instances of pseudo-epitheliomatous hyperplasia rather than true malignant neoplasia. McAnally *et al.*[71] reported 2 cases in which metastasis occurred from a malignant lesion in a chronic osteomyelitic sinus; these added to the 9 cases reported in the literature make 11 cases in which distant spread occurred. It is proposed that the regional lymph nodes be treated with Roentgen rays and that even a prophylactic dissection of these nodes be considered. The transitional epithelium from the erratic glands of the anal crypts probably invades the *fistula in ano* tracts, and this may account for the fact that acini are located in some of the fistulous tracts which have shown malignant change. Three such cases are presented in the McAnally group series. Malignant diseases occurring in a chronic empyemic sinus is a surgical rarity. There was one case in McAnally's series.

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PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF NOVEMBER 20, 1956

INFORMAL SEMINAR ON CARDIAC OUTPUT

Inter-relationships Among Cardiac Output, Stroke Work and Ventricular Contractile Force. MARION DEV. COTTEN, PH.D. AND HARRIET M. MALING, PH.D. (Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda, Maryland). The relationships existing among the cardiac stroke work, ventricular contractile force and output were studied in the heart-lung preparation of the dog. The ventricular contractile force was measured with a special strain gauge device which permitted measurement of the contractile force at the initial diastolic fiber length existing at the time of measurement. Systemic output (cardiac output minus coronary blood flow) was determined with a Shipley-Wilson rotameter while atrial and aortic pressures were measured with Statham transducers. All recordings were made synchronously on a Grass multichannel oscillograph. Stroke work and ventricular contractile force were increased by: (a) progressively increasing atrial pressures in graded increments (b) progressively raising the aortic resistance and (c) norepinephrine. A linear, or slightly curvilinear, relationship existed between the stroke work and ventricular contractile force irrespective of the manner in which the stroke work and contractile force were increased and the relationship was similar for the right and left ventricles. On the other hand, the systemic output did not always bear a linear relationship to the stroke work or contracile force. Only when the aortic pressure and heart rate were maintained constant was there a direct relationship between the systemic output and stroke work or contractile force as in the experiments in which the atrial pressures were raised progressively. However, when the aortic resistance was increased with constant inflow pressure and heart rate, the systemic output decreased while the stroke work and contractile force increased.

Effect of Various Anesthetic Agents on Cardiac Output. E. M. GREISHEIMER, PH.D., M.D., D. W. ELLIS, A.B., AND G. H. STEWART, B.S. (From the Departments of Anesthesiology, Physiology and Medical Physics, Temple University School of Medicine). Cardiac outputs by dye dilution technique using the cuvette oximeter, have been determined in dogs. When sodium thiopental, cyclopropane and ether were used without premedication, the cardiac output was highest under ether. When the same agents were used after premedication with morphine sulfate, the output remained unchanged under sodium thiopental, decreased under cyclopropane and increased under ether.

When hexobarbital, kemithal and thiamylal were used, the cardiac outputs were lower than with thiopental, the lowest being found under kemithal.

The cardiac output under viadril was high. Under chloralose-urethane it was low.

The effect of adding a second anesthetic agent was observed. When thiopental was supplemented with cyclopropane, the cardiac output decreased. When thiopental was supplemented with ether, the cardiac output increased, but not to as great an extent as when cyclopropane was supplemented with ether.

The dogs breathed spontaneously throughout the experiments. They inspired oxygen for about half an hour before the initial cardiac outputs were determined, and continued to inspire it throughout six successive observations. It seemed to make no difference whether oxygen was inspired from a spirometer or whether it was administered by means of an anesthetic machine. In the latter case, a flow of 150 to 300 ml. of oxygen per minute was maintained, according to the size of the dog.

Under all agents observed, the cardiac output rose on successive determinations. Marked rises were found under ether without premedication, cyclopropane after morphine, viadril, chloralose-urethane, and kemithal. Moderate increases were found under ether after morphine, thiopental alone, hexobarbital, and thiamylal. The least increases were found under cyclopropane alone and under thiopental after morphine.

The Effect of Increased Blood Volume on Cardiac Output and Right Ventricular Stroke Work. T. G. Schnabel, Jr., M.D., B. Thomasson, H. Eliasch and L. Werko (St. Eriks Hospital, Stockholm, Sweden). Intravenous infusions of 10% dextran in 5% glucose and water or isotonic saline solution were given at a rate of approximately 25 ml./minute for 20 to 60 minutes to normal individuals and patients with mitral stenosis. Blood volumes, determined from the change in arterial hematocrit, were increased as much as 25% in patients with mitral stenosis and up to 30% in normal subjects. Right atrial mean pressure, which was within normal limits prior to the infusion was markedly increased in all instances reaching 7 or 8 mm. of mercury. Cardiac output remained unchanged in patients with mitral stenosis with increases in blood volume of 15%. Further increases in blood volume were associated with a gradual increase in cardiac output. In normal subjects cardiac output was unchanged in those patients receiving dextran in 5% glucose and water but rose somewhat towards the end of the infusions in subjects receiving dextran in isotonic saline solution. Right ventricular stroke work increased in the patients and normal subjects but the increase in work was often small when compared to the change in right atrial pressure. It appears that in normal subjects and in patients with mitral stenosis increases in volume associated with considerable elevation of right atrial mean pressure may not always lead to an increase in cardiac output.

Effects of Exercise on Cardiac Output. J. M. Bishop, M.D., M.R.C.P. (Department of Medicine, University of Birmingham, England). Minute to minute measurements of cardiac output have been made during exercise and subsequent recovery, both in normal subjects and in patients with a variety of pathological states. The A–V oxygen difference was followed throughout by sampling mixed venous blood from the pulmonary artery 2 to 3 times a minute and arterial blood less frequently from the brachial artery. Blood oxygen saturation of each sample was measured by a spectrophotometric method. Expired gas was sampled from a side arm and collected in a spirometer. Exercise was performed in the supine position on a bicycle ergometer.

In normal subjects a new level of mixed venous blood oxygen saturation was established within a minute of the commencement of exercise. Cardiac output and A–V oxygen difference increased during the first minute of exercise but did not change significantly during subsequent minutes and resting levels were regained equally rapidly when exercise ceased. In 16 subjects cardiac output was related in a linear fashion to oxygen uptake.

Most of the disabled patients with rheumatic heart disease showed abnormally low values for mixed venous blood oxygen saturation, a large A–V oxygen difference and impairment of the normal cardiac output increase with exercise. Nevertheless a steady state was achieved almost as rapidly as in normal subjects and it is not considered necessary to prolong exercise beyond 5 minutes in order to obtain valid measurements of cardiac output. Some of these patients, studied again 9 months after mitral valvotomy, showed marked changes in the response of cardiac output to exercise in the direction of normality.

Patients with hyperkinetic states due to anemia, hyperthyroidism and systemic arteriovenous shunts were found to have an abnormally large cardiac output for the level of exercise performed. Despite the large changes in cardiac output during early exercise a steady state was achieved as rapidly as in normal subjects.

SUMMARIO IN INTERLINGUA

(See page 367 for original article)

Studios Clinic in Re un Agente Vasopressori: Metaraminol (Aramina) III. Observationes Relative a Su Uso Oral in le Tractamento de Hypotension

Doses unic de metaraminol (aramina) esseva administrate a 16 voluntarios normotensive in un studio preliminar del action de iste agente vasopressori post su administration per via oral. Le effectos vasopressori post doses adequate esseva potente e prolongate, e le effectos lateral esseva negligibile. Le efficace dosage oral esseva cinque a sex vices le quantitate requirite in injectiones subcutanee e intramuscular.

Subsequentemente metaraminol esseva administrate per via oral in le tractamento de 35 patientes qui habeva hypotension symptomatic ab varie causas. Le responsa al therapia indicava que iste methodo de administrar le droga es practic, efficace, e secur in le majoritate del casos. Su valor esseva specialmente apparente in patientes in qui un retardate recuperation ab lor hypotension esseva associate con infectiones systemic, infarcimento myocardial, prolongate periodos de allectamento, o un stato de recuperation post-operatori. Minus bon esseva le successo in le tractamento de patientes qui habeva chronic hypotension orthostatic del typo idiopathic o hypotension postural connectite con disturbationes neurologic. Le observationes del presente serie indica que le tractamento in patientes del ultimo-mentionate gruppo es satis difficile e non sin risco, sed a vices, il es ver, illo es frappantemente profitabile.

BOOK REVIEWS AND NOTICES

MEDICINAL CHEMISTRY. VOLUME II. Edited by F. F. BLICKE AND C. M. SUTER. Pp. 311. New York: John Wiley & Sons, Inc., 1956. Price, $10.00.

FIVE years have elapsed since the appearance of the first volume of this series which is being published under the auspices of the Division of Medicinal Chemistry of the American Chemical Society. Each contribution summarizes the available information on chemical compounds which have been tested for a particular pharmacologic effect. Methods for chemical synthesis and pharmacologic testing are outlined and structure-activity relationships are discussed. In this volume the subjects include: the chemical aspects of cardiac glycosides and a supplementary survey of many plant glycosides which were obtained in the search for steroids which could be converted into cortisone; synthetic estrogens; analgesics which are arylpiperidine derivatives; and β-haloethylamine adrenergic blocking agents. This volume contains an extremely large collection of data of interest to medicinal chemists and pharmacologists. S. E.

LANDMARKS IN THE HISTORY OF HYGIENE. By HENRY E. SIGERIST, M.D., D.LITT., LL.D., D.SC., F.R.C.P., Research Associate in History of Medicine, Yale University. Pp. 78; 4 ills. New York: Oxford University Press, 1956. Price, $3.00.

A SERIES of five lectures delivered in 1952 under the Auspices of the Heath Clark Foundation at the University of London. After a delightful foreword, the author is at his excellent best as the medical historian in the first three lectures: Galen's Hygiene; The *Regimen Sanitatis Salernitatum* and some of its Commentators, and the Quest for Long Life in the Renaissance. But he loses his objectivity when in the last two (Johann Peter Frank, a Pioneer of Social Medicine; and The Changing Pattern of Medical Care) he carries his usual torch for the Social State. There are references to the quality and subvention of medical care in the United States and the Soviet Union, many of them derogatory to the former, none to the latter. Of voluntary insurance schemes in the United States he says they "of course reach only a relatively small percentage of the population." It is not enough to give a blind man "a pension, a white stick and a dog . . . he must be able to maintain his self-respect, and this can be done, as the Soviet Union has unmistakably demonstrated." In the United States, while the author was there, "large sections of the population had no medical care at all or certainly not enough of it." He refers to the "red scare from which many countries are still suffering." He states that "the unlimited free choice of a physician is a fiction." He closes with the accolade: "You in England have gone a long step forward by passing the National Health Act." Yet there is a significant change in his thinking when he sees in practice the things which from the ivory tower appeared so ideal: "Now that I am back in Europe, I am no longer in favour of health insurance (*i.e.* compulsory). . . . In many European countries (it) has become rigid . . . is in the hands of groups that have vested interest. . . . The machinery is frequently very clumsy. . . ." R. K.

ELECTROCARDIOGRAPHIC TEST BOOK, VOLUMES 1 AND 2. Edited by TRAVIS WINSOR, M.D. Pp. 167 and 132 respectively; illustrated. New York: The American Heart Association, Inc., 1956. Price, $5.00 for the two volumes.

THIS book is sponsored by the Committee on Professional Education of the American Heart Association. It is apparently intended for the student or practitioner who has completed an elementary course in electrocardiography. The editor is fortunate in having obtained an advisory and review panel of 28 well-known American electrocardiographers.

The book consists of two volumes. Volume 1 contains Part A, 119 electrocardiograms with questions; Part B, 237 questions on electrocardiographic interpretation and Part C, tables outlining the quantitative range of the normal electrocardiogram. The answers to Parts A and B are given in Volume 2.

Volume 2 also contains a short case summary accompanied by a photograph of a chest film. This reproduction is poor. It is also unfortunate that the cardiothoracic ratio is employed (after apologies by the editor) because the stamp of the American Heart Association may tend to revive and imply validity of a method the reliability of which was utterly refuted a generation ago.

Instruction utilizes the multiple question technique. The reviewer believes that at least

the last third of the electrocardiograms should have no electrocardiographic hints in order to simulate the actual practice of electrocardiography.

Only two typographical errors were found: miocardial (p. 112) and V2 (for V5, p. 47). The arrhythmia in V4 (p. 38) is not explained. Coronary vasoconstriction (p. 31) is questionable.

These personal opinions and minor criticisms in no way detract from the book's value. The electrocardiographic illustrations are unusually clear. The questions are appropriate and the answers sound. The editor is particularly commended for stressing that a definitive diagnosis cannot always be made. The questions on electrocardiographic interpretation range through a remarkably large fraction of the practical aspects of this discipline.

No one is qualified to interpret electrocardiograms who cannot answer all questions posed in this book. In this sense, therefore, all students and practitioners should master the book before attempting to tackle more specialized books or to interpret a patient's electrocardiogram. L. S.

THE STRUCTURE AND FUNCTION OF SKIN. By WILLIAM MONTAGNA. Pp. 356; 116 ills. New York: Academic Press, Inc., 1956. Price, $8.80.

MONTAGNA has collected in a small space much knowledge of the microscopic anatomy of skin. The histology, cytology, histo-chemistry and electron microscopy of this organism are dealt with under the following headings: The General Anatomy of Skin; the Epidermis; the Eccrine Sweat Glands; the Apocrine Sweat Glands; the Pilary System; the Sebaceous Glands; the Dermis and Reflections. The material, compiled by a man who contributed much to our information in this field, is sufficiently detailed for the interested student to use as a base for further study. The references are numerous, and except for some the Reviewer feels would have been included were the author a dermatologist, they cover the subject well. The illustrations are superb. The Indices are well made. The inaccuracies are few. An unfortunate one is in the title of an outstanding text on Physiology and Chemistry of the Skin. Occasionally, the language is somewhat stilted and ambiguous, "inhomogeneous" and "indifferent cell" for equipotential cell. A serious omission is the absence of a section on the Nails. The author summarizes his thesis in a scholarly manner in the chapter marked "Reflections." This is a good beginning in this area of anatomy and will serve well all who read it. H. B.

MEDITATIONS ON MEDICINE AND MEDICAL EDUCATION, PAST AND PRESENT. By I. SNAPPER, M.D. Pp. 138. New York: Grune & Stratton, Inc., 1956. Price, $3.75.

AN entertaining, instructive and thought-provoking book by a man of proven talent as clinician, teacher and investigator, with a cosmopolitan breadth of vision, a sense of humor and a splendid command of language. The first chapter is a charming historical sketch of the early Dutch settlements in America and of the physicians, surgeons and midwives who served them. The second chapter is a fine appraisal of the great Dutch clinician and exponent of bed-side teaching, Boerhaave of the University of Leyden, and his influence on medical education in the United States. The third chapter is a keen analysis of the development of medical teaching in this country, with particular attention to the trend toward separation between clinical medicine and research in medicine: a schism that is related to the "full-time" program for heads of clinical departments; and with a splendid presentation of the value of a "geographic full-time" program to heal that schism. Every physician will find this book good reading, but it is a "must" for all teachers in the clinical departments and for all deans of medical schools. R. K.

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE. By ELI H. RUBIN, M.D., Professor of Clinical Medicine, Albert Einstein College of Medicine. Pp. 288; 92 ills. Springfield, Ill.: Charles C Thomas, 1956. Price, $12.50.

AN interesting and novel approach to the presentation of certain diseases of the lungs, this text is primarily devoted to concomitant conditions involving the respiratory tract initially or as a participant in the course of systemic diseases, as opposed to primary disorders of the lungs or secondary conditions such as emboli or metastatic neoplasms. There are chapters on roentgenographic chest surveys, diseases of metabolism, diseases of the blood, allergic disorders, the collagen diseases, diseases of the skin and mucous membranes, abdominal diseases, cardiovascular diseases, thoracic roentgenography, pitfalls in Roentgen diagnosis and laboratory and exploratory aids. Here is ample proof that the "silent" chest does not necessarily contain healthy lungs, nor the "noisy" chest connote

serious disease. The numerous illustrations are all well done. R. K.

THE PREMARITAL CONSULTATION. A MANUAL FOR PHYSICIANS. BY ABRAHAM STONE, M.D., AND LENA LEVINE, M.D. Pp. 90; 11 ills. New York: Grune & Stratton, Inc., 1956. Price, $3.00.

IN past years a couple contemplating marriage would never have considered consulting a physician as part of premarital preparation, and if they had the doctor probably would not have known how to proceed. Marriage counselling was not considered in the medical schools and there were no worthwhile publications on the subject. Today such consultations are sought frequently and many articles, pamphlets and books have been published but none is as informative and practical as "The Premarital Consultation" by Stone and Levine. The authors are both outstanding marriage counsellors and have drawn on their extensive experience in the field in preparation of this book.

The purpose of the premarital conference and the material to be considered are discussed and a hypothetical interview with a young couple is presented to illustrate the techniques of history taking, examination and subsequent discussion. The authors emphasize that the premarital consultation is more than a physical examination but rather presents a unique opportunity to explore attitudes toward marriage and to discuss the emotional, economic and social as well as the physical aspects of family existence. Basic principles of genetics and the inheritance of certain defects and diseases are considered in one short chapter. In a valuable Appendix marriage and birth control laws for each state are outlined.

The material is presented concisely but in detail and the style is interesting and lucid. Although this book is directed toward physicians any individual who does any form of marriage counselling could profit from studying it. J. W.

TEXTBOOK OF OCCUPATIONAL THERAPY: WITH CHIEF REFERENCE TO PSYCHOLOGICAL MEDICINE. BY EAMON N. M. O'SULLIVAN, B.A., M.B., D.P.M. Pp. 319; 17 figs. New York: Philosophical Library, Inc., 1955. Price, $10.00.

THIS is a detailed text intended primarily for occupational therapists and personnel of allied interests. The history of Occupational Therapy, purposes, methods and organization are thoroughly covered, with special reference to its application in psychiatric illness. W. S.

THE SHOULDER AND ENVIRONS. BY JAMES E. BATEMAN, M.D., F.R.C.S.(C), Orthopaedic Consultant, Sunnybrook Hospital, Toronto. Pp. 565; 376 ills. St. Louis: C. V. Mosby Co., 1955. Price, $16.25.

IN the opinion of this Reviewer, this is a comprehensive text. However, the presentation is such that it is a worthwhile text for the student, intern, resident, general practitioner and specialist. The author clearly exposes that so-called shoulder pain may not only originate about the glenohumeral joint, but also the cervical spine or the central nervous system, or both, a fact which may demonstrate that there are other lesions of an organic nature besides various phases of "subdeltoid bursitis."

The section on embryology and applied physiology is well done, and certainly both fundamental and understandable for the clinician.

The scope of clinical entities discussed runs the complete gamut. It was pleasing to find more than usual facts relevant to postural disturbances about the shoulder, a condition often misdiagnosed and mismanaged in the experience of this Reviewer.

The illustrations are sufficient and very lucid. The therapy for the conditions described is complete and up-to-date from the conservative and radical standpoint. The feature of differential diagnoses in table form of common entities discussed in each chapter is certainly a worthwhile feature.

The author is also cognizant of the doctor's responsibility in medicolegal matters, as is proven by his final chapter on management and assessment of disability in the shoulder region.

I consider this a very worthwhile text.

A. S.

THE BUBONIC PLAGUE AND ENGLAND. AN ESSAY IN THE HISTORY OF PREVENTIVE MEDICINE. BY CHARLES F. MULLETT, M.A., PH.D. Pp. 401. Lexington: The University of Kentucky Press, 1956. Price, $9.00.

THIS is an outstanding contribution in the field of English as well as medical history. The author, a layman, is a historian of long experience and with a background of many years of study of English quarantine laws. The result is a detailed story of the career of plague in its contemporary

setting and of its profound influence upon every aspect of English life. It begins in 1349 when the black rat brought the first great outbreak to London (40,000 cases with 20,000 deaths), and continues well into the 18th century, including the story of the island quarantine laws of 1721, inspired by the outbreak at Marseilles in 1720 and affecting British policy for many years thereafter. Even medical historians are content to mention only a few extreme outbreaks, like that of 1667, yet for two centuries the disease was rarely long absent from one place or another in the British Isles. General historians all too often ignore the disease. So the author is moved to indignant comment over their failure to note the outbreak of 1636 when 10,000 died in London alone: "Pages for ship-money, not a word for pestilence!" (The reviewer reacts sympathetically to that comment: he has felt the same frustration over the failure of the writers of military history to appraise the role of disease even in recent experience.) The author has set a splendid example for other historians. R. K.

Die funktionelle Diagnose der Geburt. By Dr. Hans Baumm. Pp. 76; 29 ills. Munich: J. F. Lehmanns Verlag, 1956. Price, DM 6.

In this monograph, the author describes the palpatory methods for determining the position of the presenting part in the maternal pelvis before and during labor. He favors external, rather than internal, examinations both for determining position and for estimating the depth to which the fetal head has descended into the pelvic cavity. While it is true that such examinations can be both adequate and accurate few physicians will agree with his statement "the better the obstetrician, the less frequent the internal examination."

The methods of examination are described clearly and in detail and illustrated by photographs and line drawings. Most physicians should be completely familiar with the information contained in this book but nevertheless it does emphasize the fact that much can be learned from external palpation. J. W.

Die Kolposkopie in der Praxis. By Privatdozent Dr. Med. Herbert Cramer, Universitats-Frauenklinik, Frankfurt-am-Main. Pp. 103; 120 ills., 40 in color. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $7.15.

Colposcopy has been used extensively in Germany since Hinselmann introduced the technique almost 30 years ago but it has never been popular in this country. In the last few years, however, colposcopic examination has been performed in a few large clinics in the United States, particularly in the study of cervical lesions.

Cramer, who has had extensive experience in the use of the colposcope, suggests that all cervical lesions should be studied through the instrument because it is possible to make reasonably accurate diagnoses by inspection alone. Small areas of atypical epithelium or even preinvasive cancer which might be overlooked in the ordinary examination can be detected. The final diagnosis, however, rests with biopsy and tissue examination.

The use of the instrument is described and cervical lesions are illustrated in 40 excellent color plates, each of which is accompanied by a labeled descriptive line drawing and a photomicrograph of the lesion. Anyone contemplating using the colposcope could learn much from this monograph. J. W.

Treatment of Heart Disease. A Clinical Approach. By Harry Gross, M.D., F.A.C.P., Attending Physician, the Montefiore Hospital, Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; and Abraham Jezer, M.D., Attending Physician, the Montefiore Hospital, Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons. Pp. 549; 91 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $13.00.

The authors ask themselves "why another?" (book on cardiology). This book, they say, is a presentation of therapy in heart disease based upon sound physiologic principles. They add that they intend to reach the general physician who, imbued with the physiologic point of view, may more readily understand the symptoms and clinical course of his patients. These excellent intentions suggest that the title of the book is too restrictive.

Actually, the authors have written a textbook on cardiology with emphasis on treatment. The book is divided into Part I, devoted to the pathologic physiology of myocardial insufficiency, digitalis, quinidine, arrhythmias, congestive heart failure and diet in heart disease; Part II, to hypertension and arteriosclerotic heart disease; Part III, disease of the heart secondary to inflammation; Part IV, to congenital heart disease; Part V, to

surgery in the cardiac patient; Part VI, to disease of the heart secondary to metabolic diseases; Part VII, to emotions, readjustment and rehabilitation in heart disease and an Appendix containing diet, recipes and tables of sodium and potassium contents of food.

Approximately half of each chapter is devoted to the general aspects of a subject and half to its treatment. In general, the approach is conventional and modern. There is a tendency to neglect the clinical aspects of a disease. Thus, the clinical characteristics of the hypertensive heart are completely omitted although laboratory aspects such as electrocardiographic and radiologic features are included. There is a tendency to erect straw men (for example, digitalis p. 36) to emphasize a discussion and also a tendency to substitute the author's undocumented impressions (p. 186) for reports in the literature.

Nevertheless, the book can be recommended for the general physician although it is not superior (even in its discussion of treatment) to other American textbooks of cardiology already available. L. S.

MANAGEMENT OF DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM. BY LOUIS T. PALUMBO, M.D., Chief, Surgical Service, Veterans Administration Hospital, Des Moines. Pp. 186; 23 ills. Chicago: Year Book Publishers, Inc., 1955. Price, $5.00.

THIS little book, one of the General Practice Manuals, presents, as the author says in his preface, "in a simple and concise manner, the present knowledge of the anatomy and physiology of the autonomic nervous system and its application to the medical and surgical management of a variety of diseases." It should appeal to everyone in the practice of medicine, particularly those who because of the pressure of a busy practice have time for only short but quite adequate discussions of various aspects of medicine. It should be particularly appealing to medical students who have so little time and so many things to learn.

Included are discussions of the anatomy, physiology and pharmacology of the autonomic nervous system, each in a chapter. The remainder of the contents is concerned with the various disorders of that part of the body and their management. Some may find parts to differ with, such as the value of stellate ganglion blocks in cerebral thrombosis but this is bound to happen in a discussion of a subject where striking advances have been made so recently so that time enough has not elapsed for final evaluation, if such is ever accomplished. S. G.

A FOLLOW-UP STUDY OF WAR NEUROSES. BY NORMAN Q. BRILL, M.D., Professor of Psychiatry and Superintendent and Medical Director of The Neuropsychiatric Institute, University of California School of Medicine, Los Angeles, California, AND GILBERT W. BEEBE, PH.D. Statistician, Follow-up Agency, Division of Medical Sciences, National Research Council, Washington, D.C. Pp. 393; 11 ills. Washington: V. A. Medical Monograph, January, 1955. Price, not given.

THIS rather detailed and laborious study is the result of a co-operative effort on the part of government and civilian medicine.

It was begun while the senior author was Assistant Chief, Neuropsychiatric Section of the Veterans Administration and was concluded with the help of the Veterans Administration National Research Council and two hundred co-operating psychiatrists.

With the ever present threat of total mobilization confronting us, this work produces valuable and timely information for consideration as to the selection of military personnel, the nature of neuroses as seen in the services, their treatment, prognosis and subsequent utilization of those who have incurred psychiatric disability while in service. O. E.

ALCOHOLISM AS A MEDICAL PROBLEM. Edited by H. D. KRUSE, M.D., Executive Secretary, Committee on Public Health, The New York Academy of Medicine. Pp. 102. New York: Paul B. Hoeber, Inc., 1956. Price, $3.00.

THIS is a record of a conference sponsored by the New York Academy of Medicine and the New York State Mental Health Commission. Participants were thirty outstanding representatives in the fields of psychiatry, public health, sociology, neurology and industrial medicine. The objectives of this conference, and thus of the book, were to introduce the problems of alcoholism to the physician, to create in him an appreciation of the magnitude of the disease; to encourage him to assume responsibility to the alcoholics and to stimulate research on the causes of the disease and on the care and treatment of the patients.

This small volume contains, first a discussion of the epidemiology of alcoholism. Next the causes of alcoholism are considered from four points of view: the organic; the psychodynamic; the behavioristic; and the sociologic.

The book then reveals the natural history of alcoholism with its organic and psychologic manifestations and, finally, it considers methods of evaluation of the treatments of alcoholism, in the hope that this may lead to an improvement in the level of studies in this field.

As must be true in any recording of a conference, there is a certain amount of repetition throughout the book. This is not objectionable, however, and on the whole should be of value to those persons in any field of endeavor who come in contact with problem drinkers.

An adequate Index is included. O. E.

HORMONES HYPOPHYSAIRES SOMATOTROPE ET CORTICOTROPE CROISSANCE MÉTABOLISME. By H. TUCHMANN-DUPLESSIS, Faculty of Medicine, Lille, France. Pp. 320; 59 ills. Paris: Masson et Cie, 1956. Price, 2,200 fr.

THIS book presents a well edited summary of our present knowledge of the physiology, both normal and disturbed, of the hormones of the anterior part of the pituitary gland. It is divided into two parts, the first, slightly shorter, dealing with the somatotropic or growth hormone, the second, with the corticotropic hormone. The various interrelationships of the target glands and tissues are fully discussed and documented. Full information is given regarding the nature and methods of preparation of the hormones discussed and of their many metabolic and chemical actions. In addition their clinical application is given in a conservative and critical manner. The author believes that "without exaggerated optimism, the use of hormones from the anterior hypophysis will give new impetus to clinical endocrinology and holds in store for it even more brilliant successes than those already attained." The volume is well-printed and illustrated and written in clear straightforward French, which, from the point of view of vocabulary, gives preference to the international scientific vocabulary and is hence easy to read. J. L.

CLINICAL UROLOGY. By OSWALD SWINNEY LOWSLEY, M.D., Late Director, Department of Urology, New York Hospital, and THOMAS JOSEPH KIRWIN, M.D., Professor of Urology, New York Medical College. 3rd ed. Two volumes, pp. 985; 599 ills. Baltimore: Williams & Wilkins Company, 1956. Price, $32.50, the set.

THIS book covers the various urological phases of disease in a most complete and comprehensive fashion. It is beautifully illustrated by Mr. William Didusch, the leading medical artist of this era. The two volumes are well organized, with separate chapters on normal anatomy and physiology of each part of the genito-urinary tract, as well as separate chapters on both the pathological changes and concerning the surgical treatment (in detail) of these areas. There is also a much needed chapter on diseases of the adrenal gland, a topic conspicuously absent in most urological texts.

The only weakness of this work lies in the tendency to overemphasize the importance of certain operative procedures developed by the authors but not universally accepted. Thus, Lowsley's surgical treatment of sexual impotence and of Peyronie's disease might be accepted by the uncritical reader as a standard and recommended procedure. For this reason, this work serves best as a reference and guide for urologists at or above the resident level than as a text for medical students or interns. K. C.

EPILEPSY AND THE LAW. By ROSCOE L. BARROW, Dean, University of Cincinnati College of Law, and HOWARD D. FABING, M.D., Chairman, Legislation Committee, American League Against Epilepsy. Pp. 177. New York: Grune & Stratton, Inc., 1956. Price, $8.50.

THE authors have reviewed the laws applying to epileptics in this country in the areas of: sterilization and marriage license laws, stating that hereditary transmission of epilepsy is a recessive of little account; and driver's license and workmen's compensation laws, recommending changes which would encourage epileptics, because of "fairer" treatment, to declare themselves, get proper treatment, and lessen the likelihood of becoming public charges. There are also comments regarding criminal responsibility and other laws. The authors make definite recommendations with appendices of model legislation. Anyone who has an interest in improving the legal position and decreasing the stigma attached to epilepsy should find this easily-read book of value. F. H.

CRYPTOCOCCOSIS. By M. L. LITTMAN, M.D., PH.D., Mt. Sinai Hospital, New York, and LORENZ E. ZIMMERMAN, M.D., Veterans Administration, Armed Forces Institute of Pathology. Pp. 205; 82 ills. and 4 color plates. New York: Grune & Stratton, Inc., 1956. Price, $8.50.

According to the preface, this monograph is the first of a series on the fungus diseases. If *Cryptococcosis* is a sample of what is to follow, a valuable collection of mycologia is in the making. For the idea was a good one, namely to describe each disease in a separate monograph-atlas. And the execution is even better. Dr. Littman, already a first-rank contributor to mycology literature, has culled from more than 500 source references a highly readable and concise text. Practically all the photographs are originals, most of them excellent.

The coverage is complete. And a good balance is maintained from the historical background through clinical aspects (human and veterinary) pathology, laboratory features and treatment, so that this volume will be equally helpful to the student, practitioner, teacher and researcher. To make sure nothing was omitted the authors included an addendum of miscellaneous information, added an Appendix detailing useful media and staining procedures, and finally assembled a 22-page Index. E. S.

Cancer of the Lung, An Evaluation of the Problem. Proceedings of the Scientific Session, Annual Meeting, November 3–4, 1953, American Cancer Society, Inc. Pp. 322; 131 ills. New York: American Cancer Society, Inc., 1956.

Thirty-eight authorities discuss various aspects of a disease "that is well on its way toward the proportions of a national epidemic."

Dorn and Horn review the vital statistics. The possible etiologic role of tobacco is presented by Wynder and Hammond. Their findings are subjected to some very pointed questioning by Gilliam. Air pollution, occupational factors, genetics, geography and the production of tumors in experimental animals receive appropriate attention.

Detection is covered by three papers on the results of various mass roentgenographic surveys. Other diagnostic aspects discussed include exfoliative cytology, exploratory thoracotomy and super-voltage roentgenography.

Churchill, Pool and Ochsner present various approaches to surgical resection. Irradiation and chemotherapy are reported by Hare, Schultz, Trump and Karnofsky.

The volume is paper-bound, clearly multigraphed; most of the illustrations, which are isolated in a separate section, are reasonably intelligible. References are included with only half a dozen of the papers.

Two useful ends are well served. Information scattered widely in the recent literature is brought together, and attention is focused on the current lack of knowledge of every fundamental aspect of this increasingly important disease. R. C.

Medicinal Chemistry. Volume III. Edited by F. F. Blicke and R. H. Cox. Pp. 346. New York: John Wiley & Sons, Inc., 1956. Price, $10.50.

The third volume of this series contains summaries of the chemical-biological literature on the following chemical groups: methadone and related analgesics, quarternary ammonium germicides, nonmercurial diuretics, and synthetic analogs of physostigmine. Brief introductions to the subjects are followed by extensive tables of biological effectiveness of the compounds grouped according to chemical structure. The reviewers have done a most valuable service in making readily available so much information. The editors should be encouraged to extend the reviews over the whole field of medicinal chemistry as rapidly as possible. S. E.

Sports Injuries Manual for Trainers and Coaches. By Donald F. Featherstone, M.C.S.P. Pp. 130; 25 ills. New York: Philosophical Library, Inc., 1956. Price, $4.75.

The care of the present-day athlete is largely in the hands of nonmedical qualified personnel for whom this timely manual has been written. The author has outlined, in a language that can easily be understood, what might well be considered the minimal basic knowledge of the musculo-skeletal system these individuals should possess. He has directed attention to the majority of injuries common to athletes with careful consideration being given to their prevention. This section of the manual is worthy of attentive study by coaches and trainers alike.

The methods recommended for treatment and management of the injured athlete are in keeping with those of better organized and well supervised athletic departments. The discussion of the psychological aspects and recommendations for rehabilitation and return to competition of the injured athlete merit utmost consideration of all coaches.

In the sections devoted to more serious and miscellaneous sports injuries, an omission has been made which might well be included, namely, visceral injuries, especially those of the kidney and spleen which, while very in-

frequent, do occur and may carry with them serious consequences.

This manual should prove a useful adjunct to every athletic organization, be it high school, sand lot or professional. H. F.

DERMATOLOGY. By DONALD M. PILLSBURY, M.A., D.Sc.(HON.), M.D., Professor and Director of Department of Dermatology, University of Pennsylvania School of Medicine, WALTER B. SHELLEY, M.D., PH.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine, and ALBERT M. KLIGMAN, M.D., PH.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine. Pp. 1331; 1117 ills. Philadelphia: W. B. Saunders Company, 1956. Price, $20.00.

THIS new volume reflects the combined years of experience of three dermatologists pre-eminent in the clinical field as well as in teaching and separate research interests. Together, with a small number of collaborating contributors employed to good advantage, they have provided a timely and definitive text and source book.

The work is divided equitably in sections devoted to basic principles, allergy and hypersensitivity, principles of diagnosis, dermatologic therapy and cutaneous medicine. This latter (clinical) section represents about 70% of the content. Outstanding are the chapters on mycology and bacteriology; the entire sections on diagnosis and therapy; and in the clinical section, the chapters on dermatitis and eczema, infections, tumors and psychocutaneous medicine are of special interest.

The format, classifications employed, lucid discussions and illustrations are particularly agreeable. The preface is most readable as well as important to the book. The authors have accomplished their purpose in presenting dermatology in a rational (and novel) manner and in stressing its intimacy to medicine as a whole. The book is well suited to teacher and student, practitioner and specialist; a splendid text that well merits its one word title. G. R.

HUMAN OVULATION AND FERTILITY. By EDMUND J. FARRIS, PH.D., Wistar Institute of Anatomy and Biology. Pp. 159; 35 ills. Philadelphia: J. B. Lippincott Co., 1956. Price, $6.50.

THE author has long been interested in these problems and has contributed much to our knowledge of normal human reproduction, its failures and how to correct them. In this book he reviews his work on the determination of ovulatory time and the use of this information in aiding barren couples to conceive. He has developed a rat ovarian hyperemia test by which, according to Farris, the day and almost the hour of ovulation can be predicted precisely. By using this test he has determined that ovulation occurs on about the same day in each cycle of any individual woman. The cycles vary so little that in most individuals the length can be determined with reasonable accuracy by averaging the length of any consecutive three. He disagrees with the idea that ovulation usually occurs about 2 weeks premenstrually and that the post ovulatory phase of the cycle is of relatively standard length, regardless of the interval between periods. Seventy-six per cent of his patients conceived during the three days mid-cycle.

As a result of his studies he advises the following schedule for infertile couples in whom there is no obvious abnormality which would prevent conception: 1) Calculate average length of cycle by averaging three consecutive ones and divide by two to determine mid-cycle day. 2) Coitus on three consecutive days starting two days before mid-cycle for four months. 3) Coitus on three consecutive days starting three days before mid-cycle for four months. 4) Coitus for three consecutive days starting one day before the mid-cycle for four months.

In addition he considers various methods for improving abnormal ovulation and presents his test for pregnancy which is based upon the color reaction of the cervical mucosa. The last chapter "Information of Value to the Barren Couple" is particularly good.

Although many workers question the accuracy of the Farris test for pregnancy, the author's excellent results in the management of infertile couples cannot be discounted. This book contains much information of great value to physicians who are faced with the problem of helping barren women conceive. J. W.

NEW BASES OF ELECTROCARDIOGRAPHY. By DEMETRIO SODI-PALLARES, M.D., Chief of the Department of Electrocardiography at the National Institute of Cardiology of Mexico; Professor of Cardiovascular Clinics at the National University of Mexico, Mexico City, with the collaboration of ROYALL M. CALDER, M.D., Editor, English Translation; Clinical Professor of Medicine, Graduate School, Baylor University. Translated from recent revision of 3rd Spanish edition. Pp.

727; 523 ills., St. Louis: C. V. Mosby Co., 1956. Price, $18.50.

THIS book is said to be the first Mexican book translated into English. Sodi-Pallares was fortunate to have Calder translate his book into clear idiomatic English, that, considering the subject matter, is unusually easy to read and to understand. The one regret the reviewer has, which he believes is shared by the author, is that Frank N. Wilson is not here to read the book.

For Sodi-Pallares has remained devoted to his teacher and his teachings. This book is essentially an exposition of the Wilsonian School greatly extended by the author's own important contributions derived particularly from his studies of intracavitary electrocardiography. The author does not overlook the importance of the blood and its pressure within the heart and systemic factors in the genesis of a person's electrocardiogram.

Because this book is concerned with the electric phenomena of the heart, the first chapter is logically devoted to the principles of electricity and the second to electrophysiology. So that the general reader may not be discouraged or confused, the mathematical basis for concepts are in an Appendix at the end of the book. Individual succeeding chapters are devoted to electrical axis, unipolar leads, injured muscle, precordial leads, the activation process of the heart and the electric and anatomic position of the heart.

Vectorcardiography is discussed concisely yet adequately. The author states that "at the present time, a V C curve can add very little, if any, to the information supplied by a well interpreted electrocardiogram."

The author concludes, after a chapter on the ventricular gradient, with one on the intracavitary potential, his own contribution.

There are, perhaps, many electrocardiographers who will disagree with the rigid interpretation of the anatomic source of the electrocardiographic curves, but none can fail to admire the conceptual scheme which unifies the entire book and which has proved so useful in the application of electrocardiography to clinical practice. Every cardiologist should be familiar with this book.

If there are other books like this in Mexican medicine, the reviewer pleads for their translation. L. S.

PLASTIC REPAIR OF GENITO-URINARY DEFECTS. By GEORGE BANKOFF, M.C., D.CH., F.R.C.S. ED., F.R.F.P.S., Honorary Surgeon, Italian Hospital, London. Pp. 355; 86 ills. New York: Philosophical Library, Inc., 1956. Price, $17.50.

THE title "Plastic Repair of Genito-Urinary Defects" does not indicate all the material the author attempts to present in his text. In one chapter, devoted to Physiology of Reproduction, he discusses coitus, fertilization and sex hormones, and in a relatively long section entitled Sterility and Impotence, these subjects are considered, but inadequately.

The major portion of the text is devoted to a discussion of the surgical correction of congenital and acquired disorders of both male and female genito-urinary tracts. The embryological development and anatomy of the various organs are well discussed, in fact this probably is the best part of the entire book. The correction of the anomalies, however, is less well done. In many instances a series of diagrams of an operative procedure is presented but no mention of the operation is made in the text. The reverse is also true; many operations are described sketchily but are not illustrated. The methods presented are in general acceptable, but the author often does not indicate which ones are the most successful, which he prefers and which he has found unsuitable.

I doubt that the author's hope that the book will become "as well thumbed, dog-eared and marginally annotated, and as much of a guide, philosopher and friend in daily work, as were the note-books of student days," will be fulfilled. J. W.

NEW EDITIONS

Clinical Unipolar Electrocardiography. By BERNARD S. LIPMAN, A.B., M.D., Instructor in Medicine, Emory University School of Medicine, and EDWARD MASSIE, A.B., M.D., Associate Professor of Clinical Medicine, Washington University School of Medicine. 3rd ed. Pp. 397; 325 ills. Chicago: The Year Book Publishers, Inc., 1956. Price, $7.50.

THIS book began as a booklet "Unipolar Electrocardiographic Notes" prepared for the students of Washington University School of Medicine. It gives a brief diagnostic presentation of the unipolar concept of clinical electrocardiography developed primarily by Wilson and his students. In this edition, the authors have added chapters on ventricular gradient, vectorcardiography and vectorelectrocardiography. They have included an atlas of 194 electrocardiograms. The book remains a booklet.

The reviewer does not approve of the publication of such booklets for two reasons. A booklet for medical students of a medical college is prepared with the knowledge that dis-

cussions between instructors and students will help to clarify the limitation and significance of the didacticism in the booklet. More important, there appears no need for an elementary book on a fragment of clinical electrocardiography. There are available excellent elementary books on electrocardiography which include more information on unipolar electrocardiography than this booklet and at no greater cost.

The reviewer may be wrong because this book has reached its third edition. L. S.

Technical Methods and Procedures of the American Association of Blood Banks. Revised edition. Pp. 111. Minneapolis: Burgess Publishing Co., 1956. Price, $3.00.

THIS is an authoritative manual on blood bank methods and procedures. It is clearly and concisely written, and, in addition, the interpretative discussions appear to be quite adequate. It is recommended for all hospital blood banks, as well as for physicians and medical technologists concerned with the technical aspects of blood transfusions. C. Z.

Stuttering: Significant Theories and Therapies. BY EUGENE F. HAHN, 2nd edition prepared by ELISE S. HAHN, University of California at Los Angeles. Pp. 180. Stanford: Stanford University Press, 1956. Price, $4.00.

THIS book is a revised edition of the text written in 1943 by the late Dr. Hahn. The theme of the 2nd edition remains the same as in the first, that is, to present a compendium of theories concerning the etiology and treatment of stuttering. The second edition contains three new contributors and three have been omitted that appeared in the first edition. In addition, a number of the authorities have rewritten their presentations and in some cases have modified their opinions since the 1943 publication. Stuttering causation is discussed from organic, psychologic and semantogenic points of view. Therapeutic applications of these theories are also discussed. While this book is lacking in bibliographical information and critical analysis, it will be very valuable to students of speech pathology and medicine who want to have an understanding of the complexities of the stuttering problem. M. H.

NEW BOOKS

Physiological Studies of Infantrymen in Combat. NELLO PACE AND A LARGE GROUP, University of California. Pp. 47, 7 ills. Berkeley: University of California Press, 1956. Price, $1.25.

THIS study is a detailed analysis of the altered physiological patterns in an intensive combat situation of both short and long duration. Both anticipation and acute combat during 18 hours provoke adrenal cortical responses which last for at least 12 hours. This and other parameters measured represent valuable data. M. O.

Franz Joseph Gall, Inventor of Phrenology and His Collection. BY ERWIN H. ACKERKNECHT, M.D. AND HENRI V. VALLOIS, M.D. Pp. 86; 9 ills. Madison, Wisconsin: Department of History of Medicine, University of Wisconsin Medical School, 1956. Price, $1.50.

THIS monograph is the first in a series, "Wisconsin Studies in Medical History." Of medical historical interest, it reviews the life and work of Franz Joseph Gall (1757–1828). Remembered today for the obsolete doctrine of phrenology, Gall also did basic work in anatomy, psychophysiology, anthropology and social reform. A catalog of his anatomical collection, preserved in Paris, is included in this work. F. R.

Sleep. BY MARIE C. STOPES, D.SC., PH.D. Pp. 154. New York: Philosophical Library, Inc., 1956. Price, $3.00.

THIS is a book reflecting the opinions of an interesting and dynamic personality known already in the field of medicine for her work on marital problems and who, in this book, writes on the subject of sleep. She quotes liberally from poets and other writers, and gives some of her own opinions on the subject. For example, "Personally, I think it is a crime of the first magnitude to wake anyone, save in an emergency. I should lay down as an absolute rule that no child should be waked, not even a child of school age:" Again, "People who find difficulty in going to sleep and have used all the usual dodges without success might try the effect of a large grandfather clock in the bedroom A small quick-ticking grandfather clock is of no use. Before buying it, test it by having its ticks and your own heart-beats per minute each counted when you have been sitting in a chair for five minutes. Unless the clock ticks are materially slower than your own heart beat, don't buy it." There are chapters on "Sleep at Different Ages" and "Insomnia." While the book is more philosophical than scientific it may have some helpful ideas for the general physician on a subject and a symptom that plagues many. O. E.

Journal of the American Medical Association Queries and Minor Notes. Pp. 334. St. Louis: C. V. Mosby Co., 1956. Price, $5.50.

QUERIES and Minor Notes that appear regularly in the pages of the Journal of the American Medical Association are so widely read that descriptive comment is hardly necessary. But here, in one volume, is a collection of the same published during the twelve months ending June, 1955. The items have been carefully selected and organized for general interest and usefulness. They are arranged and indexed according to the standard nomenclature of diseases and operations.

Because of the extreme diversity of the subject matter, this book will have a wide range of

appeal; from the specialist to the lay person. The Queries represent a cross-section of the problems general practitioners meet and cannot readily solve. For this reason, they have a special value. The replies are instructive and thorough within the necessarily limited scope. In many instances more than one consultation is offered showing variable approaches to the same problem. There is much to enjoy and learn from these pages for the average reader. H. H.

Dictionary of Poisons. By Ibert Mellan and Eleanor Mellan. Pp. 150. New York: Philosophical Library, Inc., 1956. Price, $4.75.

Judging from the introductory remarks, this book is intended to serve laymen in a first aid capacity. In the reviewer's opinion this book is inadequate as a sole reference for either lay or professional people. It has no index. The poisons are arranged alphabetically; one can find curare, histamine, and cinchona but not lye, mothballs, furniture polish, bleaching agents, or many other common household or industrial items. One can find opium readily but not paregoric. Less space is devoted to aspirin than curare, and pituitary posterior occupies as much space as gasoline or camphor. Directions are given for the preparation of six emetics, seven demulcents, and four cathartics but not for Universal Antidote. The authors do advise reading labels, and under the treatment for most poisons is a final caution, "Call a physician." Interesting historical notes are included for some of the poisons. R. S.

Interprofessional Cooperation for the Improvement of our Health and Welfare. Papers delivered at a Conference on Health and Rehabilitation, the third in a series of Anniversary Celebrations, January, 1956. Pp. 125. Milwaukee: Marquette University Press, 1956.

This small volume, which is not for sale, contains interesting and provocative opinions on present-day medical practices as they are seen from the standpoints of medical schools, dentistry, Public Health, hospital administration and so on. An impressive group of speakers contributed to this symposium for which Marquette University is to be congratulated.

To any one interested in the educational, philosophical and sociologic aspects of medicine, this book will provide enjoyment and stimulation.

W. S.

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